

**ROLE OF CHEMOTHERAPY IN  
ADVANCED MALIGNANT DISEASES**

**THESIS**  
FOR  
**MASTER OF SURGERY**  
( GENERAL SURGERY )



**BUNDELKHAND UNIVERSITY  
JHANSI (U. P.)**

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1989

**RISHI BHATIA**


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C E R T I F I C A T E

This is to certify that the work entitled  
"ROLE OF CHEMOTHERAPY IN ADVANCED MALIGNANT DISEASES"  
which is being submitted as thesis for M.S. (General  
Surgery) examination, 1989 of Bundelkhand University,  
by DR. RISHI BHATIA, has been carried out under my  
guidance and supervision. His results and observations  
have been checked and verified by me from time to time.

He has put in the necessary stay in the  
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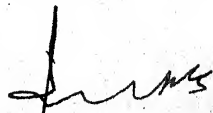
( GUIDE )



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I take the privilege to dedicate this work for the cause of suffering humanity with the hope that "cure" of cancer will be achieved shortly in this exciting era of therapeutic research.

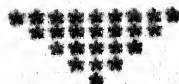
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( RISHI BHATIA )

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## INTRODUCTION



## INTRODUCTION

For centuries a bitter duel is being fought by the mankind by every available means to ward off the most threatening enemy known to life : Cancer. Incidence of cancer in India is becoming high while in other countries deaths from cancer are second to cardiovascular diseases' accident. Despite of tremendous efforts cancer has still not been checked. The basic question of the cause and course of the malignant disease is one on which it can be claimed, without exaggeration, that a great many advances have been made in recent decades.

In the treatment of cancer, one of the basic assumption is that all malignant cells should be destroyed, removed or neutralized to achieve cure. Whether successful treatment has to eradicate all neoplastic cells or bring the cell number down to a level that can be controlled by the host's supposed immunologic defences against the tumour, is unknown at present. Five therapy modalities exist today which can be used in an attempt to bring about the requisite malignant cellular reduction : surgery, radiotherapy, endocrinotherapy, chemotherapy and immunotherapy.

Cancer can be classified into two major categories : solid tumors and haematologic malignancies. Solid tumours are initially confined to specific tissue or organ sites. In time, however, cancer cells break off from the original tumour mass, enter the blood or lymph system, reach to distant parts of the body, and start secondary growth there (metastasis). When this occurs, the disease is in the disseminated stage. Conversely, haematologic malignancies involve the blood and lymph systems, and for this reason, they are frequently disseminated diseases from the very beginning.

In solid tumours, surgery, and/or radiotherapy are the traditional, primarily chosen treatments. Neither modality, however, can be considered curative, once disease has metastasized beyond the local region (primary site and nearby lymph nodes) or has involved a vital organ extensively. Chemotherapy is relegated almost exclusively to secondary or tertiary treatment of solid tumours i.e. when surgery and radiotherapy fail. Conversely in haematologic malignancies, chemotherapy is the treatment of choice at diagnosis.

There are many approaches to treat a patient with cancer. Despite the many advances in cancer surgery and radiotherapy since the turn of the century, there has been no significant decrease in the mortality in most cancers. While chemotherapy of most cancers has not yet

become of equal importance to surgical and radiation management, there are several neoplasms for which drugs are the treatment of choice. The initiation of systemic chemotherapy in patients with evidence of disseminated disease is predicted upon the fact that in many patients symptoms will be ablated and in a few patients life may be prolonged.

The principles of cancer therapy are based on our knowledge of the biology of tumour growth. The realization, two decades ago, that even small primary cancers shed, viable tumour cells into the circulatory system as they grow in their primary site, fundamentally altered the thinking about the likelihood of eradicating cancers using methods of local control alone and led to the development of systemic method of treatment, i.e. chemotherapy.

The chemotherapy of malignant disease refers to the use of cyto-toxic drugs. Cyto-toxic drugs are general cellular poisons which have a deleterious effect, to a greater or lesser degree on normal cells and a variety of tumours. Because these drugs are potentially lethal, cancer chemotherapy is largely a compromise between toxic and therapeutic effects. While giving chemotherapy we need to consider seriously the relative differential sensitivity of normal versus cancer tissues. So very special type of selectivity and localisation of drug action is of paramount importance.



Recently, chemotherapy has proved to play increasingly important role in the management of malignant diseases, particularly where surgery or radiotherapy can not give complete cure. The reason often given for the present day emphasis on chemotherapeutic research is that surgery and radiation therapy have reached the limits of their capacities to cure cancer. Radiotherapy and surgery offer ways of reducing the tumour mass in specific regions of the body amenable to surgical excision or high doses of radiotherapy. Neither is applicable to do the destruction of the widely disseminated or circulating tumour cells characteristically present in most patients with cancer. Chemotherapy can be tried in every form of malignant disease either localized, disseminated or circulating tumour cells.

In the past few years a number of chemotherapeutic agents have been evaluated for the treatment of cancer. Unfortunately at present no chemotherapeutic regimen either single or combination can be considered as "standard" for the treatment of cancer. However, a number of different classes of chemotherapeutic agents can produce measurable regressions in the malignancy of various organs. Excellent results have been seen in some malignancies, e.g. Hodgkin's disease, chorio carcinoma, chronic leukaemia and testicular teratoma. Good and sometimes exceptional results are also attainable in ovarian carcinoma, histiocytic lymphoma and

Burkitt's lymphoma. Promising results have been seen in carcinoma of breast, and soft tissue sarcomas.

Better results in recent years have been due to improved methods of applying cyto-toxic drugs as well as to the introduction of new drugs, combination chemotherapy and multi-modality treatment. Having these incentives, the present work was conducted in various groups of patients. As cancer is becoming increasingly common in the Bundelkhand area and we are getting lots of cases of malignancies in early stages as well as in late stages, where surgery is out of question and radiotherapy has only limited and at the most palliative role, it was decided to try chemotherapy in all cases to assess it's role as curative agent or for palliation use.

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REVIEW OF LITERATURE

## REVIEW OF LITERATURE

The use of chemical agents to control the growth of malignancies goes back to the earliest history of medicine. The first cancer chemotherapeutic agent potassium arsenite (Fowler's solution) was used by Lissauer in 1865 in the treatment of chronic leukaemia. In 1893 Coley used repeated inoculations of erysipelas (Coley's toxins) for the treatment of malignant tumour. Herbst and Loeser (1941) had trials of hormones for treating carcinoma of prostate and breast. Alteration of hormonal status and effect of castration, as a method of treatment for prostatic cancer was studied by Huggins & Hodges (1941).

Drug development for cancer began with the accidental identification of the lympholytic activity of mustard gases used in World Wars I and II. In World War I, it was noticed that the mustard war gases that were used because of their vesicant action on skin and mucous membranes also had toxic effects on other tissues, especially the haematopoietic system. In 1918 at a base hospital in France, severe leukopenia was observed in patients 9 days after they had been exposed to mustard gas. Eventually investigators recognized that these systemic effects might also reduce the number of malignant cells in certain cancers - in particular, the leukaemias and lymphomas.



In 1931, Adair & Bagg published the results of treatment with alcoholic solutions of mustard gas (dichloro diethyl sulphide). They referred to the observations of James Ewing and others on the destructive nature of burns caused by the gas and used it on tumours involving skin. It was applied topically in 12 cases and injected into the tumour in 1, a recurrent neurogenic sarcoma. The tumour regressed and remission of a few months were obtained in other patients. Hopes were expressed for the future use of mustard gas in cases of localised disease. Chemically, the nitrogen mustards differ from the mustard war gases only in that a nitrogen replaces sulphur.

In early 1940, under the office of Scientific Research and Development with the chemical Warfare Services of the United States Army, extensive investigation of the toxicology of the nitrogen mustards were made. In 1942, Goodman and Gilman were studying the pharmacology of nitrogen mustard derivatives (methyl chloro ethylamines) and noted their effects on lymphoid tissue and dividing cells. The two compounds which received attention were known by the code names HN<sub>2</sub> and HN<sub>3</sub>, the latter trichloro triethylene, being the first used clinically (Goodman et al, 1946). Clinical trials with HN<sub>2</sub>, mustine hydrochloride (nitrogen mustard, mechlorethamine hydrochloride), were initiated in 1943 in the United States and the results were reported by Rhoads in 1946. Finally, in 1945 to 1946 during early clinical trials at an army hospital, nitrogen



mustard was demonstrated to be the first chemotherapeutic agent (Alkylating agent) used to successfully treat Hodgkin's disease. Jacobson and his co-workers (1946) introduced nitrogen mustard in the treatment of cancer. The use of this agent was based on its recognized markedly suppressive effect on the haemopoietic and lymphoid tissue.

Because all of the successfully treated patients subsequently relapsed, the initial success in the treatment of Hodgkin's disease and lymphocytic lymphoma with this drug was followed by an over-whelming disappointment and skepticism that cancer could be successfully treated by drugs. Further excitement was created with the identification of the effectiveness of the antimetabolite methotrexate, first used successfully against acute childhood leukaemia and then in the treatment of choriocarcinoma. During this period, the antimetabolites were developed when researchers discovered that a slight modification of the structures of folic acid made it a growth - arresting metabolic antagonist. Farber began clinical trials with folic acid antagonists in the 1940's and study of the effects of folic acid metabolism on leukaemic cells resulted in the second cytotoxic drug of therapeutic value - the antifolate (anti-metabolite) methotrexate. In this instance, remission produced by the drug appeared permanent.

The need for a standardized approach to the development of anticancer drugs was recognised in the 1950s.

Since then, many synthetic drugs, fermentation, and plant products have been identified as possessing antitumour activity against rodent tumours. These compounds have been selected both by rational synthesis and random screening.

In Anti-metabolics group - Purine analogues were developed and the results with mercaptopurine were published by Burchenal and others in 1953. The pyrimidine analogue fluoro-uracil (5-Fluoro-uracil) went into clinical trials in 1958 (Heidelberger C. et al) and later thioguanine and others were tried and introduced into clinical use. Antitumour activity of cytosine arabinoside was reported by Evans J.S. et al (1961). A new fluorinated pyrimidine (Ptorafur) has been developed in the U.S.S.R., extensively tested in Japan, and is now under evaluation in the U.S.A. (Blokhina N.G. et al, 1972).

Amongst alkylating agents Mustine and trichloro-triethylamine were used parenterally (Goodman et al, 1946; Rhoads, 1946). The first oral alkylating agent was tretamine (triethylene-melamine, TEM) and a series of oral nitrogen mustard derivatives was synthesized at the Chester Beatty Research Institute in London. Still widely used are Chlorambucil, melphalan (L-phenylalanine mustard, L-PAM) and busulphan (Haddow, A. et al, 1953). Thio-tepa (Triethylene thiophosphoramide) was utilized as an adjuvant to mastectomy in a national co-operative study under the direction of the

National Institute of Health, with doctor Rudolf Noer as Chairman (1964).

Meanwhile antibiotics were being investigated for anti-tumour properties. Actinomycin D from a strain of *Streptomyces* was shown to have anti-tumour activity in animals (Schulte, G, 1952; Waksman, S.A., 1960), and early trials in 1956 showed promise (Farber, 1960; Farber, 1966). Almost at the same time Mitomycin C was developed in Japan (Frank, W. et al, 1960) and Daunomycin (Daunorubicin) was studied by Di Marco, A. etc. (1963). Bonnadonna (1969) was the first to report activity of Adriamycin in sarcomas. Later, Adriamycin was utilized for Thyroid cancer (Cottlieb, J. et al, 1972). With the advent of Bleomycin (Blum, R.H., 1973), testicular tumours have become curable.

The plant alkaloids and Nitrosoureas were of special interest. Results of clinical trials demonstrating value of vincristine and vinblastine in Hodgkin's disease and other tumours were published in 1960 (Hodes et al, 1960; Johnson et al, 1960; Warwick et al, 1960). A new plant alkaloid VM 26 (citrovorum) was reported to be effective in lymphomas (1972), glioblastoma (Sklansky, B, et al, 1973) and intracerebral L1210 leukaemia (Muggia, F. et al, 1971). Among N itrosoureas Carmustine (BCNU), Lomustine (CCNU) and Semustine (methyl CCNU) have shown variable response rate in advanced gastro-intestinal cancer (Moertel, C.G., 1973), while Streptozotocin is the only drug which has been



meaningfully evaluated in carcinoma of pancreas (Broder, L.E., 1973).

Many miscellaneous agents have shown anti-tumour activity. Chemotherapy with OP' DDD (Mitotane) is now of established value in adreno-cortical carcinoma (Bergental, D.M. et al, 1960). Hydroxyurea has a place in the treatment of chronic myelocytic leukaemia (Kennedy and Yarbrow, 1966). Unique among chemotherapeutic drugs L-asparaginase is an enzyme (Broome, 1968) useful in acute lymphocytic leukaemia (Burchenal and Karnofsky, 1970; Cohen et al, 1976; Editorial, 1971). Hexamethylmelamine and Dacarbazine (DTIC) are of importance in having anti-tumour activity against ovarian carcinoma and malignant melanoma (Wilson, 1970; Luce, 1970). Procarbazine, a methylhydrazine derivative, act like an alkylating agent and is used in leukaemia; Hodgkin disease and brain tumours (Spiers, 1967; Vasantha, 1974). The ability of some platinum complexes to inhibit cell division led to their investigation as anti-cancer drugs by Rosenberg and others (1975). Cis-platinum (Platinum diamminodichloride, Cis-diammine platinum (II) has been most extensively used, being highly effective in testicular tumours and ovarian carcinomas (Gottlieb, 1975; Hill et al, 1975).

New drugs Dibromo mannitol and 5-azacytidine have been demonstrated useful in leukaemia (Canellos, G.F., 1975; Vogler, W.R., 1975). The drugs in Phase I or Phase II studies are hoped will be the new active drugs of tomorrow.

In alkylating agents, Iphosphamide is a cyclophosphamide analogue under trial for ovarian cancer, breast cancer and lymphomas (Cohen, M.H., 1973; Ahmann, D.L., 1974). Asaley, a derivative of Melphalan (phenylalanine mustard) and Galactitol, a derivative of dihalohexitol have shown response in lymphoma and breast carcinoma (Elson, L.A., 1968). Anti-metabolites Baker's antifol, a triazine antifolate (Skeel, R., 1974; Rodriguez, V., 1975); Cyclocytidine (NSC 145668) a synthetic analogue of cytosine arabinoside (Ho DH 1974, Chawla, P.L., 1974) and Diglycoaldehyde, a product of purine nucleoside, inosine (Kaufman, 1975) are under clinical trial for different malignancies. Anti-tumour antibiotics Chromomycin A<sub>2</sub> and Piperazinedione isolated from a culture of *Streptomyces* are being clinically tested in Japan, South Africa and United States (Slavick, M., 1973; Kovach, J.S., 1973; Gottlieb, J.A., 1975; Pratt, C. et al, 1975). Random synthetics cytembena (NSC 104801) and Laetrite (Amygdalin) are under observation (Carter, S.K., 1976; Frytak, S., 1975; Moertel, C.G., 1982).

At present, there are around 40 effective anti-neoplastic drugs available. The quest for new cyto-toxic drugs continues with optimum and there is still great potential for the better application of available agents.

### Combination Chemotherapy and Multi-modality Treatment

The most important aspect of cancer chemotherapy trials conducted in the 1960s and realized in the 1970s was the demonstration that drugs could cure patients with some types of advanced cancer. When in the early 1960s it was appreciated that a variety of different types of chemical could influence the progression of malignant diseases, the concept of combining drugs in twos, threes and fours was first explored. Combination chemotherapy refers to the concurrent and to some extent sequential use of several drugs in an attempt to achieve maximum therapeutic effect without increasing unduly the undesirable side effects (Carter and Soper, 1974; De Vita and Schein, 1973). The theory behind combination chemotherapy was to evaluate the hypothesis that simultaneous disruption of the metabolism of a tumour cell at more than one site might have far more profound effects on the cell than a single metabolic lesion. The most important initial goal of the more intensive drug treatment programme, was to erase all clinical evidence of disease (complete remission).

It was 1960, when Li, Whitmore, Golbey and Grabstald published the first account of treatment of testicular cancer by combination chemotherapy using chlorambucil, methotrexate and autinomycin D. Greenspan (1963) was one of the first investigators to successfully exploit the potential of combination chemotherapy in breast cancer. In 1964 the simultaneous use of vincristine,



methotrexate, mercaptopurine and prednisone, the so called VAMP treatment in acute lymphoblastic leukaemia of childhood led the way of combination chemotherapy in other forms of malignant disease (Freireich et al, 1964; Henderson, 1967; Henderson, 1969). Thereafter many workers brought out various drug combinations for different malignancies e.g. Lacher, M. et al (1965) for Hodgkin's disease, Grest, T.S. et al (1969) for Leukaemia, Cooper, R. (1969) for Breast cancer, Reitemeier, R.J. et al (1970) for gastrointestinal cancer and De Vita, V.T. et al (1970) for Hodgkin's disease.

In recent years many more regimes have been given some authoritative workers, e.g. Canellos, G.P. et al (1976) for breast carcinoma, Bull, J. (1977) for breast carcinoma, and Bonadonna, G. et al (1977) for Hodgkin's disease.

A variety of data suggest that for some diseases, cancer chemotherapy should be considered strongly as part of a co-ordinated programme of treatment involving multiple modalities including drugs, irradiation and surgery (Martin, D.S., 1973). In many situations, cytotoxic drugs are capable of shrinking only a proportion of the tumour, so increasing attention has been paid to the use of chemotherapy in conjunction with surgery or radiotherapy to lessen the total tumour load. Such use of chemotherapy is referred as "adjuvant" chemotherapy. Amongst first

reports Mrazek et al (1959) was one to report use of nitrogen mustard post-operatively in Colo-rectal carcinoma. Thenafter many workers made clinical trials in multi-modality therapy, e.g. Noer, R.J. (1961) for breast cancer; Holden, W.D. et al (1962) for GIT cancer; Longmire, W.P. et al (1968) for gastric carcinoma; Fisher, B. et al (1968) for breast cancer; Moertel, C.G. and Reitemeier, R.J. (1969) for GIT cancer and Holden, W.D. et al (1970) for colorectal cancer.

Since 1971 multi-modality treatment has advanced as much that even 100% cure has been achieved in some cases. Developments have been made in the treatment of Lung carcinoma (Hansen, H. 1972; Higgins, 1972; Laing, A.K., 1975); Head and Neck cancer (Friedman, M. et al, 1970; Lipshutz, H. et al, 1973; Goldsmith, M.A. et al, 1975); Gastro-intestinal cancer (Moertel, C.G. et al, 1976; Carter, S.K. et al, 1975); and Breast cancer (Carter, S.K., 1976; Bonadonna, G., 1976; Fisher, B. et al, 1977; Nissen-Meyer, R. et al, 1978; Bonadonna, G. et al, 1981; Rossi Anna et al, 1981; Livingston et al, 1987). Combined modality therapy has been proved very successful in GIT cancers, sarcomas of paediatric age group, Wilms tumour, ovarian carcinoma, Bronchogenic and Breast carcinoma.

Combination chemotherapy has been shown to be of great value in improving the results of treating cancer patients when compared with single agent therapy. Clinical trials have demonstrated that cancers can generally be



grouped into categories according to the effectiveness of systemic treatment (Vincent, T., De Vita, J.R., 1987). Malignant diseases can be ranked into groups comprising those for which chemotherapy contributes to cure, those for which effective control prolongs useful life and those for which benefit is less certain or unproven.

I. Tumours for which chemotherapy can be curative

- . Acute Lymphoblastic Leukaemia (childhood)
- . African Burkitt's lymphoma
- . Hodgkin's disease
- . Wilm's tumour
- . Non-Hodgkin's lymphomas (Diffuse histiocytic and nodular mixed type)
- . Testicular carcinomas (Teratomas)
- . Ewing's sarcoma
- . Rhabdo myosarcoma
- . Chorio-carcinoma.

II. Tumours in which chemotherapy prolong life

(Response rate  $\geq$  50%).

- . Acute Leukaemia (adult)
- . Breast carcinoma
- . Chronic Leukaemia
- . Myeloma
- . Ovarian carcinoma
- . Small cell lung cancer
- . Osteogenic sarcoma
- . Non-Hodgkin's lymphoma (lymphocytic type).

III. Tumours in which chemotherapy sometimes prolong life

(Response rate  $\angle$  50%).

- . Head and Neck tumours
- . Gastro-intestinal carcinomas
- . Bladder carcinoma
- . Hypernephroma
- . Endometrial carcinoma
- . Malignant melanoma.

IV. Tumours which are usually refractory to currently available chemotherapy.

- . Carcinoma oesophagus
- . Colo-rectal carcinoma
- . Squamous cell lung carcinoma.

In recent years, it has become obvious that the optimal way of treating many kinds of tumours has been by combinations of drugs. The optimal combinations of drugs for the primary therapy of advanced neoplasms and as adjuvant (ancillary) therapy with surgery and radiation therapy are still under active study at many centres for cancer research.

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## MATERIAL AND METHODS



## MATERIAL AND METHODS

In the present study, a concerted effort has been made to evaluate the role of chemotherapy in seventy eight patients having various malignancies who were thought to be candidates for chemotherapy and were admitted in M.L.B. Medical College Hospital, Jhansi.

### Selection of Patients

Criteria for selection of patients for inclusion in the study was objective. Patients suspected of having malignancy were admitted to hospital. They were subjected to thorough clinical examination including detailed history and physical examination. Relevant investigations were made to confirm the diagnosis, as well as for classification and staging of malignancy. In all cases diagnosis was confirmed by histopathological examination. Staging of the disease was done according to TNM classification. After the diagnosis and staging, patient was assessed for chemotherapy according to type and stage of malignancy and then trial of chemotherapy was begun. Those cases were selected for chemotherapy, who either were found unfit for Radiotherapy or Surgery, due to extensive spread of the disease or where disease had recurred after Radiotherapy or Surgery.

Clinical Classification and Staging - was done to plan treatment strategy and to evaluate prognosis. Standardized nomenclature given by UICC, known as the TNM system was used to know anatomic extent of disease.

T - extent of primary tumour ( $T_0, T_{1-4}$ )

N - condition of regional lymph nodes ( $N_0, N_{1-4}$ )

M - absence or presence of distant metastasis ( $M_0, M_{1-4}$ ).

After arranging T, N and M categories (with degrees of extension), these were then grouped into four clinical stages (e.g. I to IV). Alternatively typical clinical staging was done as follows :

<u>Stage</u>	<u>Primary tumour (T)</u>	<u>Regional Lymph Nodes (N)</u>	<u>Distant Metastasis (M)</u>
I	Mobile (operable)	None	None
II	Mobile (operable)	Mobile (operable)	None
III	Fixed (inoperable)	Fixed (inoperable)	None
IV	Any of above	Any of above	Present

Grouping of Patients - Depending upon organ involved, type of malignancy and stage of malignancy, following groups were made :

1. Lymphomas - (A) Hodgkins

(B) Non-Hodgkins

- |                           |               |     |
|---------------------------|---------------|-----|
| 2. Leukaemias - (A) Acute | - Lymphocytic | ALL |
|                           | - Myelocytic  | AML |
| (B) Chronic               | - Lymphocytic | CLL |
|                           | - Myelocytic  | CML |

### 3. Carcinoma Breast

### 4. Gastro-intestinal Carcinoma

- (A) Gastric Carcinoma
- (B) Colo Rectal Carcinoma
- (C) Pancreatic Carcinoma
- (D) Gall Bladder and Liver Carcinoma.

### 5. Urogenital Carcinoma

- (A) Ovarian Carcinoma
- (B) Testicular Carcinoma - Seminoma  
Teratoma
- (C) Renal Carcinoma
- (D) Prostatic Carcinoma.

### 6. Miscellaneous

- (A) Lung Cancer
- (B) Head and Neck Cancer.

Selection of drugs/Regime - There are different drugs and regimes described for various groups of malignancies. In this study, a regime was chosen after following considerations :

1. Simplicity - Regime with minimum number of drugs involved was chosen.
2. Availability of drugs - Drugs easily available locally were chosen.



3. Cost consideration - As the patients usually have spent lot of money already in the treatment, many patients could not afford costly drugs. Therefore, Regime was chosen to give maximum benefit with alternate cheap drugs.
4. Side effects/Toxicity of drug - Serious undesirable side effects are determining factors in the choice of a drug. For example, neuropathy caused by vincristine limits it's use, especially in the older patient. Vinblastine is similar and can be used instead. Daunorubicin and Adriamycin are cardio toxic.
5. Route of Administration - The oral route is convenient but unsuitable when high doses are required. High dosage usually has an emetic effect, hence a parenteral preparation was preferred when high doses were indicated. An oral drug can not be given to a patient who is vomiting, unconscious or dysphagic. When there is doubt about the patient's reliability in taking medication, the intravenous route is better method of administration. Intravenous preparation can cause a severe local inflammatory reaction if they leak from the vein into the tissues. Pain and swelling can persist at the site for a couple of weeks and the vein itself becomes thrombosed.
6. Drug dosage and schedule - The treatment objective is to provide the patient with the maximum therapeutic benefit and the minimum amount of morbidity. The

relationship between the desired and undesired effects of a drug is termed its "therapeutic index". Drug dose was chosen within a narrow range because of the dose response relationship and the low therapeutic index for most anti-tumour drugs. Depending on tolerance, dose adjustments were made for subsequent courses of chemotherapy.

The time at which drugs are given has an important influence on toxicity. Anti-tumour agents are usually used intermittently to allow re-growth of normal marrow and gut epithelium. In this way, the toxicity of a drug may be reduced and its efficacy improved.

7. Sensitivity and Resistance to Drugs - may be Primary (natural) or acquired, developing during course of treatment. So history of previous drug treatment was taken to consider sensitivity or resistance to drugs.

### Treatment Programmes

1. Single Drug Chemotherapy - Single drug was used alone when a disease was found sensitive to only one agent or its derivatives, with little or no clinical sensitivity to other types of drug. Single drug was also used alone when no extra advantage with multiple drug therapy was expected.



2. Multi drug/Combination Chemotherapy - Concurrent or sequential use of multiple drugs was made to achieve maximum therapeutic effect without increasing side effects. Drug combination was made with following criteria :

- Each drug should be active when used alone.
- Each drug should have different mode of action.
- Toxic side effects of each drug should differ.

Various regimes used for different malignancies are described ahead.

3. Multi modality Therapy (Adjuvant Chemotherapy) -

Chemotherapy was used after primary resection to prevent the growth of sub-clinical micro-metastases or prior to local therapy with surgery to reduce a tumour bulk. So multi-modal therapy was given by combining surgical or/and radiotherapeutic approaches with chemotherapy.

Various drugs/regimes used for different malignancies are as follows :

1. Carcinoma Breast

(A) For Early Breast Cancer (Adjuvant Chemotherapy)

CMF Regimen

Cyclophosphamide 100 mg/m<sup>2</sup> oral days 1 to 14

Methotrexate 40 mg/m<sup>2</sup> I.V. day 1 and 8

Fluoro uracil 600 mg/m<sup>2</sup> I.V. day 1 and 8

Repeated after 4 weeks.

Such six cycles were given.

## (B) For Advanced Breast Cancer

CMF Regimen

Cyclophosphamide	900 mg/m <sup>2</sup>	I.V.	day 1
Methotrexate	50 mg/m <sup>2</sup>	I.V.	day 1
Fluoro uracil	600 mg/m <sup>2</sup>	I.V.	day 1

Repeated after 3 weeks.

Such six cycles were given.

Cooper's Regimen (CMFVP)

Cyclophosphamide	80 mg/m <sup>2</sup>	oral	daily
Methotrexate	20 mg/m <sup>2</sup>	I.V.	weekly
Fluoro uracil	500 mg/m <sup>2</sup>	I.V.	weekly
Vincristine	1.0 mg/m <sup>2</sup>	I.V.	weekly
Prednisone	30 mg/m <sup>2</sup>	oral	daily

(Taper after 12 days)

Course was given for six weeks.

2. Lymphomas

## (A) Hodgkin's disease (Stage III &amp; IV)

MOPP Regime

Mustine Hcl.	6 mg/m <sup>2</sup>	I.V.	days 1 and 8
Oncovin (Vincristine)	1.4 mg/m <sup>2</sup>	I.V.	days 1 and 8
Procarbazine	100 mg/m <sup>2</sup>	oral	days 1 to 14
Prednisone	40 mg/m <sup>2</sup>	oral	days 1 to 14

Prednisone was given in 1st & 4th cycle only.

Treatment free interval 14 days (so one cycle was of 28 days)

Such six cycles were given.

COPP Regime

Cyclophosphamide	600 mg/m <sup>2</sup>	I.V. days 1 and 8
Oncovin (Vincristine)	1.4 mg/m <sup>2</sup>	I.V. days 1 and 8
Procarbazine	100 mg/m <sup>2</sup>	oral days 1 to 14
Prednisone	40 mg/m <sup>2</sup>	oral days 1 to 14

Prednisone was given in 1st & 4th cycle only.

Treatment free interval 14 days (so one cycle was of 28 days)

Such six cycles were given.

## (B) Non-Hodgkin's lymphoma

CVP Regime

Cyclophosphamide	400 mg/m <sup>2</sup>	oral days 1 to 5
Vincristine	1.4 mg/m <sup>2</sup>	I.V. day 1 only
Prednisone	100 mg/m <sup>2</sup>	oral days 1 to 5

One cycle consists of 21 days (so treatment free interval was of 16 days).

Such six cycles were given.

3. Leukaemias

## (A) Acute Myeloid Leukaemia (AML)

## (1) For induction of Remission

Cytosine arabinoside	100 mg/m <sup>2</sup>	I.V. 24 hrs drip days 1 to 3
Vincristine	1.4 mg/m <sup>2</sup>	I.V. day 1
Daunorubicin	60 mg/m <sup>2</sup>	I.V. days 1 to 3

Cycle repeated after 2 - 4 weeks.



## (ii) For consolidation and maintenance of Remission

Cytosine arabinoside  $100 \text{ mg/m}^2$  I.V. 24 hrs drip x 2 daysVincristine  $1.4 \text{ mg/m}^2$  I.V. x 2 daysDauno rubicin  $60 \text{ mg/m}^2$  I.V. x 2 days

Repeat course every 8 weeks.

## (iii) For CNS involvement

Cytosine arabinoside 50 mg - Intrathecal - twice a week.

Methotrexate 0.15 - 0.25 mg/kg - Intrathecal - twice a week.

 $(8 \text{ mg/m}^2)$ 

(max. dose 12.5 mg)

## (B) Acute Lymphocytic Leukaemia (ALL)

## (i) For Induction of Remission

Vincristine  $1.4 \text{ mg/m}^2$  I.V. weeklyPrednisone  $40 \text{ mg/m}^2$  oral daily

Given for 4 - 6 weeks.

Patients not responding to above treatment, add also

Dauno rubicin  $25 \text{ mg/m}^2$  I.V. weekly x 3 weeks.

## (ii) For Maintenance of Remission

Methotrexate  $25 \text{ mg/m}^2$  oral twice weeklyMercaptopurine  $50 \text{ mg/m}^2$  oral daily

Both are given for 3 months.

After every 3 month, Vincristine and Prednisone are given for two weeks in same dose and schedule as in Induction therapy.

Such cycles are given for atleast 2 years.



## (iii) For CNS involvement

Prophylaxis Methotrexate  $12 \text{ mg/m}^2$  (max. 15 mg) intrathecal.

Preventive Methotrexate  $12 \text{ mg/m}^2$  (max. 15 mg) intrathecal  
twice weekly for 3-5 doses.

## (C) Chronic Myeloid Leukaemia (CML)

## (i) For Induction of Remission

Busulphan (Myleran) 4 - 8 mg oral daily

Given usually for 3 - 6 weeks (max. 12 weeks) till TLC  
is 20,000/cmm.

For Refractory cases, add

Mercaptopurine 50 mg/day for 5 days every week.

Given for 4 - 6 weeks.

## (ii) For Maintenance

Busulphan 2 - 4 mg oral daily

Till TLC comes to 10,000 - 12,000/cmm.

Treatment was stopped when TLC was below 10,000/cmm.

After stopping drugs, therapy was resumed when TLC  
increased above 15,000/cmm.

## (D) Chronic Lymphocytic Leukaemia (CLL)

## (i) For Induction of Remission

Chlorambucil 4 - 8 mg/day oral

Prednisolone 30 - 40 mg/day oral

Given for 6 weeks with adjustment of doses according to  
TLC Report.

## (ii) For Maintenance

Chlorambucil 2 - 4 mg/day oral

Prednisolone 15 - 20 mg/day oral

Given for 3 - 6 months (Prednisone was stopped after total 12 weeks).

4. Gastro-intestinal Carcinoma

## (A) Gastric Carcinoma.

(i) FAM Regime

Fluoro uracil	500 mg/m <sup>2</sup>	I.V. day 1, 8, 21, 28
Adriamycin	30 mg/m <sup>2</sup>	I.V. day 1, - 21, -
Mitomycin C	10 mg/m <sup>2</sup>	I.V. day 1, - - -

Treatment free interval 4 weeks.

Such 6 cycles are given.

(ii) FM Regime

Fluoro uracil	325 mg/m <sup>2</sup>	I.V. day 1, 2, 3, 4, 5.
Mitomycin C	7.5 mg/m <sup>2</sup>	I.V. day 1.

Treatment free interval 2 - 4 weeks.

Course of six cycles.

## (B) Colo-Rectal Carcinoma.

Parenteral 5 FU 15 - 20 mg/kg I.V. once weekly

Oral - 5 FU 15 mg/kg daily for 6 days

Then 15 mg/kg once weekly.

## (C) Pancreatic Carcinoma

(i) SMF RegimeStreptozotocin 1 mg/m<sup>2</sup> I.V. day 1, 8, 29, 36Mitomycin C 10 mg/m<sup>2</sup> I.V. day 1.Fluoro-uracil 500 mg/m<sup>2</sup> I.V. day 1, 8, 29, 36

Treatment free period 3 weeks (Duration of cycle 8 weeks).

(ii) FAM RegimeFluoro-uracil 600 mg/m<sup>2</sup> I.V. day 1, 8, 29, 36Adriamycin 30 mg/m<sup>2</sup> I.V. day 1.Mitomycin C 10 mg/m<sup>2</sup> I.V. day 1, 8, 29, 36

Treatment free period 3 weeks (Duration of cycle 8 weeks).

## (D) Gall Bladder and Liver

Fluoro uracil 600 mg/m<sup>2</sup> I.V. or oral for 5 days5. Uro-genital Carcinoma

## (A) Ovarian Carcinoma (stage III &amp; IV)

CMF RegimeCyclophosphamide 150 mg/m<sup>2</sup> oral day 1 - 14Methotrexate 40 mg/m<sup>2</sup> I.V. day 1 & 8Fluoro uracil 600 mg/m<sup>2</sup> I.V. day 1 & 8

Repeat every 4 weeks.

## (B) Testicular Carcinoma

PVB RegimeCis Platinum 20 mg/m<sup>2</sup> I.V. days 1 to 5 } Repeat afterVinblastine 6 mg/m<sup>2</sup> I.V. day 1 & 2 } 3 weeks



Bleomycin  $15 \text{ mg/m}^2$  I.V. weekly  
Course of 12 weeks.

(C) Renal Carcinoma

Renal Cell Carcinoma (Hypernephroma)

(1) PROVERA (Medroxyprogesterone)

200 - 800 mg oral daily

400 - 800 mg I.M. monthly

(ii) Vinblastine  $6 \text{ mg/m}^2$  I.V. once every two weeks.

Wilms tumour (Nephroblastoma)

Actinomycin D  $15 \text{ u gm/kg}$  for 3 - 5 days

Repeat after 2 weeks

Vincristine  $1.5 \text{ mg/m}^2$  I.V. weekly.

6 week course.

(D) Prostatic Carcinoma

(1) Diethyl Stilboestrol  $5 \text{ mg/day}$  1 - 3 mg oral daily.

(ii) Honvan (Posfesterol)  $0.5 - 1.0 \text{ gm}$  I.V. daily x  
5 days.

(iii) In Hormonal Refractory cases

Adriamycin  $30 \text{ mg/m}^2$  I.V. day 1

Cyclophosphamide  $100 \text{ mg/m}^2$  oral day 1 to 14.

6. Miscellaneous

(A) Lung Carcinoma

(i) Small Cell Carcinoma

VAC Regime

Vincristine  $1.4 \text{ mg/m}^2$  I.V. day 1

Adriamycin  $50 \text{ mg/m}^2$  I.V. day 1



Cyclophosphamide  $750 \text{ mg/m}^2$  I.V. day 1

Repeat every 3 weeks.

(ii) Non-small Carcinoma

FAM Regime

Fluoro-uracil  $600 \text{ mg/m}^2$  I.V. day 1, 8, 29, 36

Adriamycin  $30 \text{ mg/m}^2$  I.V. day 1,

Mitomycin C  $10 \text{ mg/m}^2$  I.V. day 1, 8, 29, 36

Treatment free period 3 weeks (Duration of cycle 8 weeks).

(B) Head and Neck

(i) Methotrexate  $50 \text{ mg/m}^2$  I.V. weekly

Bleomycin  $15 \text{ mg/m}^2$  I.V. weekly

Course of 4 - 6 weeks.

(ii) Methotrexate  $50 \text{ mg/m}^2$  I.V. weekly

Vincristine  $1.4 \text{ mg/m}^2$  I.V. weekly

Course of 4 - 6 weeks.

Follow-up and supportive care

Patients coming for follow-up of the therapy were subjected to following investigations specifically.

- Blood picture for pan-cytopenia.

- TLC and DLC to exclude Leucopenia or Leucocytosis.

Patients having TLC less than  $3000/\text{cmm}$  were not given chemotherapy.

- Platelet count was done to see thrombocytopenia. Chemotherapy was given while maintaining count above 1,00,000/cmm.
- Haemoglobin-to know anaemia.

Alongwith therapy, support to the patient was given on the following aspects.

- Treatment of fluid and electrolyte balance.
- Prevention and treatment of infection.
- Treatment of haemorrhage and anaemia.
- Psychological support.

#### Evaluation of Treatment

In order to evaluate response to treatment, following observations were made at each consultation and cycle of therapy.

- . Change in size of tumour.
- . Change in size of liver, spleen, lymphnodes etc.
- . Change in weight and appetite.
- . Change in symptoms like pain, pallor etc.
- . Performance status of patient.
- . Change in laboratory parameters.

Criteria for evaluation of response - Three criteria of evaluation of response have been adopted.



1. Objective Evaluation - was done in the following terms -

- (i) Complete Response (CR) : Complete disappearance of all known disease, determined by two observations not less than four weeks apart.
- (ii) Partial Response (PR) : 50% or more reduction in the sum of products of the longest perpendicular diameters of discrete measurable disease, with no new lesion appearing.
- (iii) No Response : Less than 50% reduction or no change in the size of lesion or increase in size of tumour less than 25%.
- (iv) Progressive disease : Appearance of any new lesion, or, 25% or more increase in size of previous lesion.

Duration of response is the period which lasts from the date when response was first recorded to the date thereafter on which subsequent response is noted.

2. Subjective Evaluation - was done on following parameters (Performance Status Scale, ECOG).

- 0 - Able to carry on normal activity.
- 1 - Able to live at home with tolerable symptoms.
- 2 - Disabling symptoms but  $\angle$  50% of time in bed.
- 3 - Severely disabled.  $\nabla$  50% of time in bed, but able to stand.
- 4 - Very ill, confined to bed.
- 5 - Dead.

3. Evaluation of Toxicity - was done in three categories.

- (i) Acute and sub-acute toxic effects - In which immediate (within seconds) and early (within hours) complications were seen.
- (ii) Chronic and late toxic effects - to observe intermediate (within days) and late (within months) complications.
- (iii) Death due to treatment.

Procedures after evaluation of response

- . On "complete or partial response", the same Chemotherapy was continued.
- . On "No Response" or "Progressive Disease", the Chemotherapy was altered in dose, schedule or components of regime.
- . On toxicity, complications or side-effects, the Chemotherapy was either stopped or dosage was reduced or change in schedule or regime was done with supportive care of patient.

\*\*\*\*\*



# OBSERVATIONS

			1.2
			1.4
			1.6
			1.8
			2.0
			2.2
			2.4
			2.6
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			5.0
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			7.6
			7.8
			8.0
			8.2
			8.4
			8.6
			8.8
			9.0
			9.2
			9.4
			9.6
			9.8
			10.0

OBSERVATIONS

In the present study cases suspected of having malignancy were admitted in the wards of M.L.B. Medical College, Jhansi (U.P.). After all possible investigations 78 cases were diagnosed as patients of cancer of different organs for chemotherapy. Number of patients in various malignancies were as follows :

Table IIncidence of malignancies.

Malignancy		Patients		
		No.	%	
Carcinoma Breast	Early	12	17	15.3
	Late	5		6.4
Lymphoma	Hodgkin's	5	12	6.4
	Non-Hodgkin's	7		9.0
Leukaemias	ALL	8	14	10.2
	AML	1		1.2
	CLL	-		-
	CML	5		6.4
Gastro-intestinal Carcinoma	Gastric	7	20	9.0
	Colo-Rectal	4		5.1
	Pancreas	4		5.1
	Gall Bladder & Liver	5		6.4
Urogenital Carcinoma	Ovarian	3	4	3.8
	Testicular	-		-
	Renal	-		-
	Prostatic	1		1.2
Miscellaneous	Lungs	5	11	6.4
	Head & Neck	6		7.7
Total		78		100.0

Most of the malignancies studied, belonged to GIT (26%) and Breast (22%). Leukaemia and Lymphoma were next to them (18% and 15% respectively). Among individual malignancies, early breast cancer (15.3%) and ALL (10.2%) were more common (Table I).

Carcinoma breast was seen more (early 42% and late 60%) in the age group of 41 - 50 years. Lymphoma was observed more in the age group of 21 - 30 years (Hodgkin's 40% and Non-Hodgkin's 57%). Acute Lymphocytic Leukaemia was more common (50%) in age group of 11 - 20 years, while CML was more (40%) in 31 - 40 years age group. Gastro-intestinal malignancies were more found above the age of 51 years. Carcinoma of ovary, lung and Head & neck were common in age group of 41 - 50 years. On average, malignancies were found more in 41 - 50 years age group (33%), as shown in Table II.



Table II

## Age-wise distribution of malignancies :

Malignancy	No. of patients	Age in years									
		0 - 10	11 - 20	21 - 30	31 - 40	41 - 50	51 & above	No.	%	No.	%
Carcinoma Breast	12	-	-	-	3 25.0	5 42.0	4 33.0	-	-	-	-
	5	-	-	-	2 40.0	3 60.0	-	-	-	-	-
Lymphoma	5	-	1 20.0	2 40.0	1 20.0	1 20.0	-	-	-	-	-
	7	-	-	4 57.0	1 14.0	1 14.0	1 14.0	-	-	-	-
Leukaemias	8	2 25.0	4 50.0	1 12.5	1 12.5	-	-	-	-	-	-
	1	-	1 100.0	-	-	-	-	-	-	-	-
	0	-	-	-	-	-	-	-	-	-	-
	5	-	1 20.0	1 20.0	2 40.0	1 20.0	-	-	-	-	-
G.I. Carcinoma	7	-	-	-	1 14.0	2 28.0	4 57.0	-	-	-	-
	4	-	-	-	1 25.0	1 25.0	2 50.0	-	-	-	-
	4	-	-	-	2 50.0	1 25.0	1 25.0	-	-	-	-
	5	-	-	-	-	2 40.0	3 60.0	-	-	-	-
	3	-	1 33.0	-	-	2 66.0	-	-	-	-	-
Uro-genital Carcinoma	0	-	-	-	-	-	-	-	-	-	-
	0	-	-	-	-	-	-	-	-	-	-
Miscellaneous	1	-	-	-	-	-	1 100.0	-	-	-	-
	5	-	-	-	-	3 60.0	2 40.0	-	-	-	-
Total	6	-	-	-	1 17.0	4 66.0	1 17.0	-	-	-	-
	78	2 2.5	8 10.0	8 10.0	14 18.0	26 33.0	19 24.0	-	-	-	-



Table III

Sex-wise distribution of malignancies.

Malignancy		No. of patients	Male		Female	
			No.	%	No.	%
Carcinoma Breast	Early	12	-	-	12	100.0
	Late	5	1	20.0	4	80.0
Lymphoma	Hodgkin's	5	3	60.0	2	40.0
	Non-Hodgkin's	7	6	86.0	1	14.0
Leukaemias	ALL	8	6	75.0	2	25.0
	AML	1	1	100.0	-	-
	CLL	0	-	-	-	-
	CML	5	4	80.0	1	20.0
G.I.Carcinoma	Gastric	7	3	43.0	4	57.0
	Colo-Rectal	4	2	50.0	2	50.0
	Pancreas	4	3	75.0	1	25.0
	Gall Bladder & Liver	5	2	40.0	3	60.0
Uro-genital Carcinoma	Ovarian	3	-	-	3	100.0
	Testicular	0	-	-	-	-
	Renal	0	-	-	-	-
	Prostatic	1	1	100.0	-	-
Miscellaneous	Lungs	5	4	80.0	1	20.0
	Head & Neck	6	4	67.0	2	33.0
Total		78	40	51.0	38	49.0

Lymphoma and Leukaemia were found more in male patients (75% and 78% respectively). In male and female incidence of cancer is 10% and 2.6% respectively. In females, breast cancer constitutes 42% of cases, Lymphoma, Leukaemia and ovarian carcinoma constitutes 5.2% each. In males, incidence of Lymphoma, Leukaemia and Gastro-intestinal malignancies range about 25% each. About 80% of cases of lung cancer were seen in males. On average, malignancy was distributed equally in male and female patients (51% and 49% respectively), as has been shown in Table III.

#### Course of Treatment

To observe the number of patients, evaluable for response of treatment, following categories were made :

- (A) Patients who took complete course.
- (B) Patients who took incomplete course, but adequate treatment.
- (C) Patients who took incomplete course and inadequate treatment -
  - 1. due to non-compliance.
  - 2. due to toxicity.

Table IV

Courses given to patients.

Malignancy		No. of patients	A	B	C <sub>1</sub>	C <sub>2</sub>
Carcinoma Breast	Early	12	3	6	3	-
	Late	5	1	2	1	1
Lymphoma	Hodgkin's	5	2	2	1	-
	Non-Hodgkin's	7	2	3	1	1
Leukaemia	ALL	8	2	4	1	1
	AML	1	-	1	-	-
	CLL	0	-	-	-	-
	CML	5	1	2	2	-
G.I.Carcinoma	Gastric	7	1	4	1	1
	Colo-Rectal	4	-	3	1	-
	Pancreas	4	-	3	1	-
	Gall Bladder & Liver	5	-	2	3	-
Uro-genital Carcinoma	Ovarian	3	1	1	1	-
	Testicular	0	-	-	-	-
	Renal	0	-	-	-	-
	Prostatic	1	-	1	-	-
Miscellaneous	Lungs	5	1	3	1	-
	Head & Neck	6	2	3	1	-
Total		78	16	40	18	4



In carcinoma breast 70% patients and in gastrointestinal malignancy 55% patients took complete or adequate treatment. Overall 72% patients took complete or adequate treatment and were evaluable for response (Table IV).

Only those patients were considered evaluable for response who took complete course and who took incomplete but adequate treatment, i.e. group A and B of Table IV.

Response of Treatment - was judged in following groups -

- CR : Complete Response
- PR : Partial Response
- NR : No Response
- PD : Progressive disease
- OR : Overall Response (CR + PR)

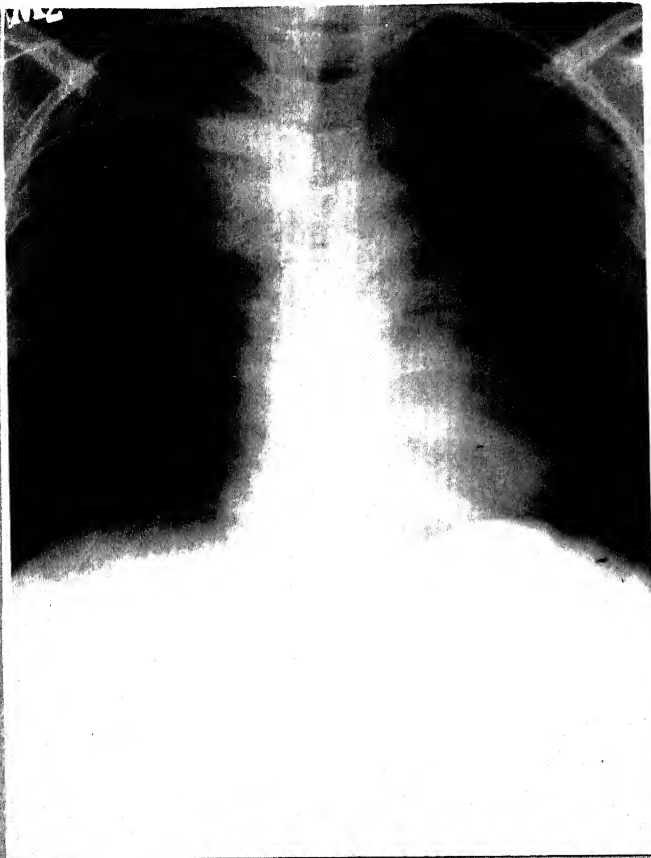
#### 1. In Lymphoma

Table V

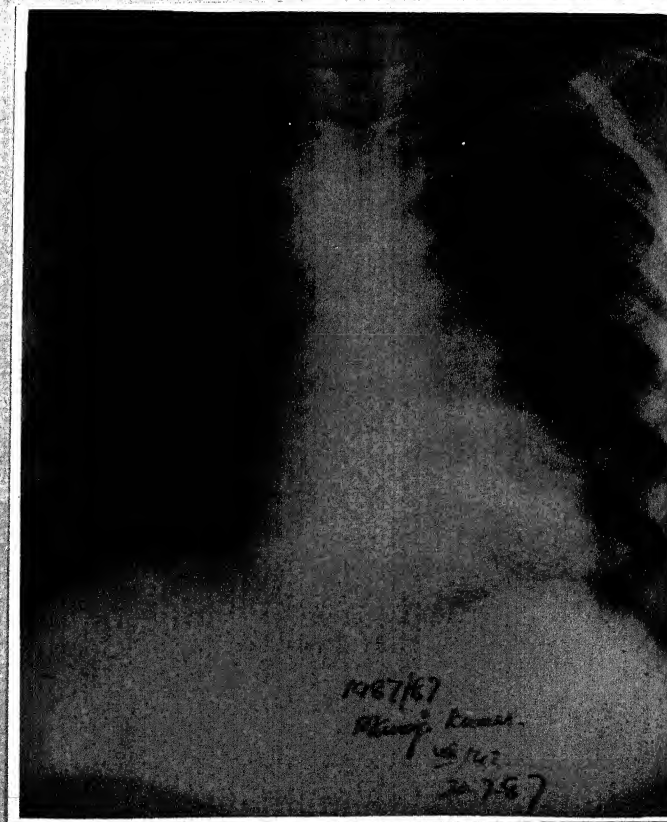
Malignancy	No. of evaluable cases	CR		PR		NR		PD		OR	
		No.	%	No.	%	No.	%	No.	%	No.	%
Hodgkin's Lymphoma	4	2	50	1	25	1	25	-	-	3	75
Non-Hodgkin's Lymphoma	5	1	20	1	20	2	40	1	20	2	40

Complete response in Hodgkin's and Non-Hodgkin's lymphoma was 50% and 20% respectively, while overall response was 75% and 40% respectively. Average response of chemotherapy in lymphoma was 55% (Table V).

Mediastinal Lymphoma



Before Treatment



After Treatment



## 2. In Breast Carcinoma

Cases which were evaluated numbered 12, out of which 9 were of early stage and 3 were of late stage. Use of adjuvant chemotherapy in early breast carcinoma after simple or radical mastectomy showed no symptom or sign of appearance of local or distant metastasis in any case, except in one case in which one small nodule appeared on stitch line and on biopsy it proved non-malignant. Till date all patients enjoyed disease-free survival.

In late stage of breast carcinoma, one case (33%) showed partial response, one case (33%) showed progressive disease and remaining one showed no response. Thus overall response was 33% in late stage of breast carcinoma.

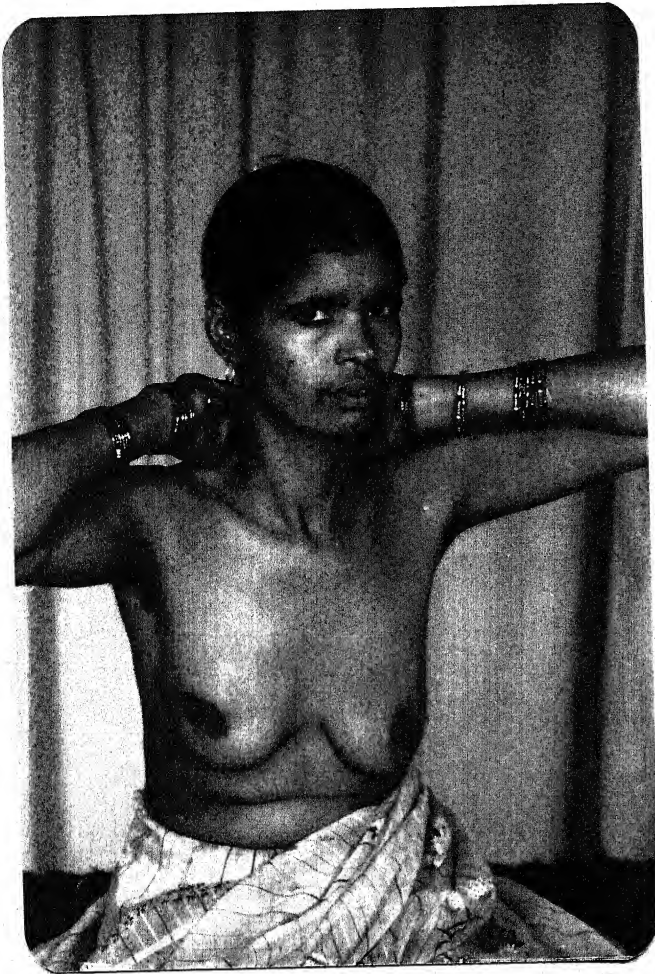
## 3. In Leukaemia

Table VI

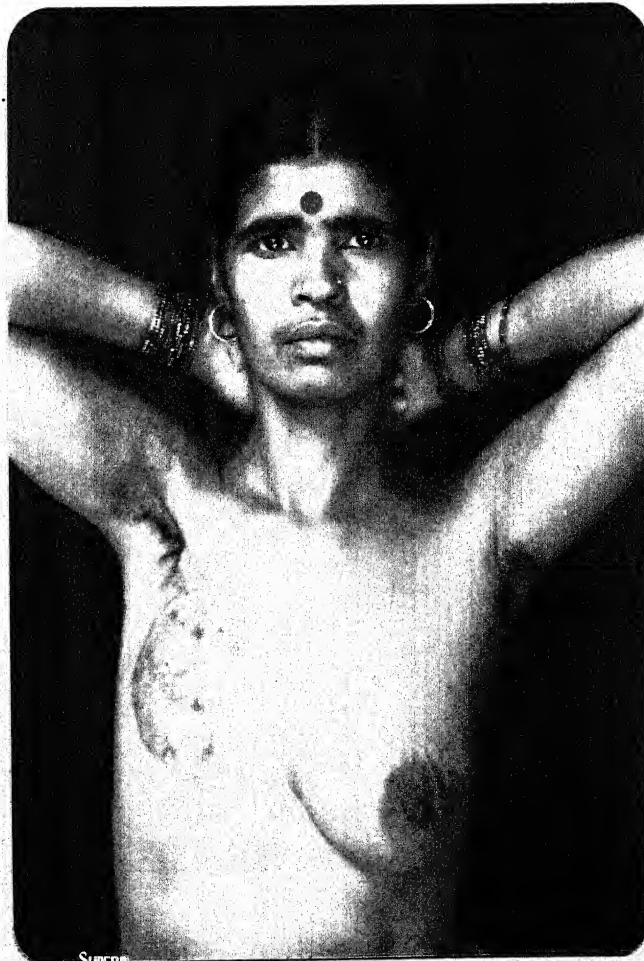
Malignancy	No. of evaluable cases	CR		PR		NR		PD		OR	
		No.	%	No.	%	No.	%	No.	%	No.	%
ALL	6	1	17	2	33	1	17	1	17	3	50
AML	1	-	-	-	-	1	100	-	-	-	-
CLL	0	-	-	-	-	-	-	-	-	-	-
CML	3	1	33	-	-	1	33	1	33	1	33



Breast Carcinoma



Before Treatment



After Treatment

In Acute Lymphocytic Leukaemia (ALL) complete response was seen in 17% cases and partial response in 33% cases, thus overall response was 50%. In CML, overall response was 33% and progression of disease was seen in one case (33%). Average response rate in leukaemia was 40% (Table VI).

#### 4. In Gastro-intestinal Carcinoma

Table VII

Malignancy	No. of cases evaluable	CR		PR		NR		PD		OR	
		No.	%	No.	%	No.	%	No.	%	No.	%
Gastric	5	1	20	1	20	2	40	1	20	2	40
Colo-Rectal	3	-	-	1	33	1	33	1	33	1	33
Pancreas	3	1	33	-	-	2	66	-	-	1	33
Gall Bladder & Liver	2	-	-	-	-	1	50	1	50	-	-

In Gastric carcinoma, 20% cases showed complete response and 20% showed partial response, thus overall response was 40%. In Colo-Rectal carcinoma and in Pancreatic carcinoma overall response was 33% in each. In Carcinoma of Gall Bladder and Liver, no response was seen in 50% cases and progressive disease was seen in 50% cases. Average response rate in gastro-intestinal carcinoma was 31% (Table VII).



# 5. In Uro-genital Carcinoma

Evaluable cases of ovarian carcinoma were two, one (50%) showed partial response and one (50%) showed no response, so overall response was 50%. In prostatic carcinoma, one patient was given hormonal therapy which responded partially.

# 6. Miscellaneous

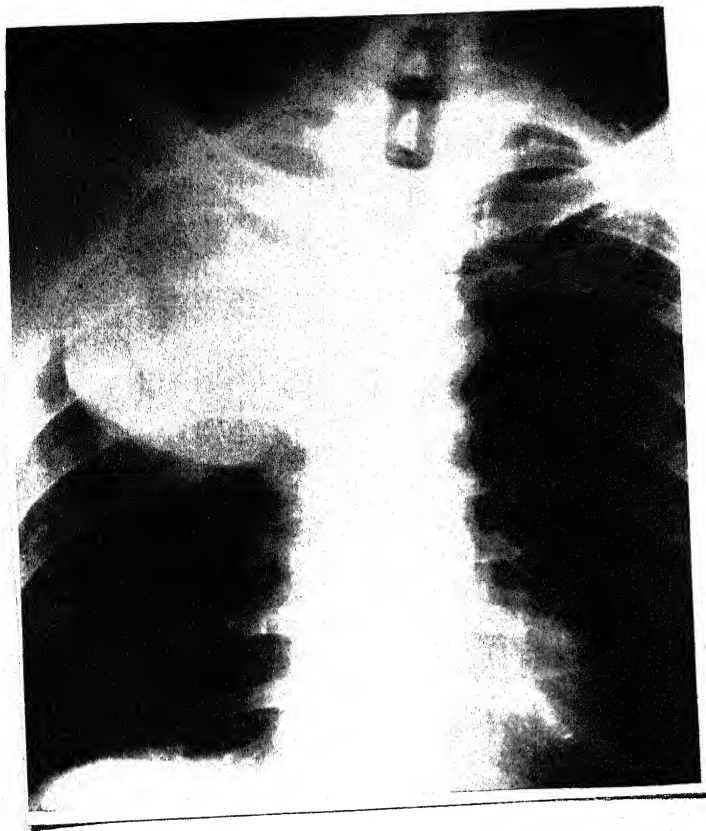
Table VIII

Malignancy	No. of patients evaluable	CR		PR		NR		PD		OR	
		No.	%	No.	%	No.	%	No.	%	No.	%
Lungs	4	-	-	1	25	2	50	1	25	1	25
Head & Neck	5	1	20	1	20	2	40	1	20	2	40

Carcinoma of the lungs showed overall response in 25% cases, while carcinoma of head and neck showed overall response 40% (Table VIII).



Lung Carcinoma

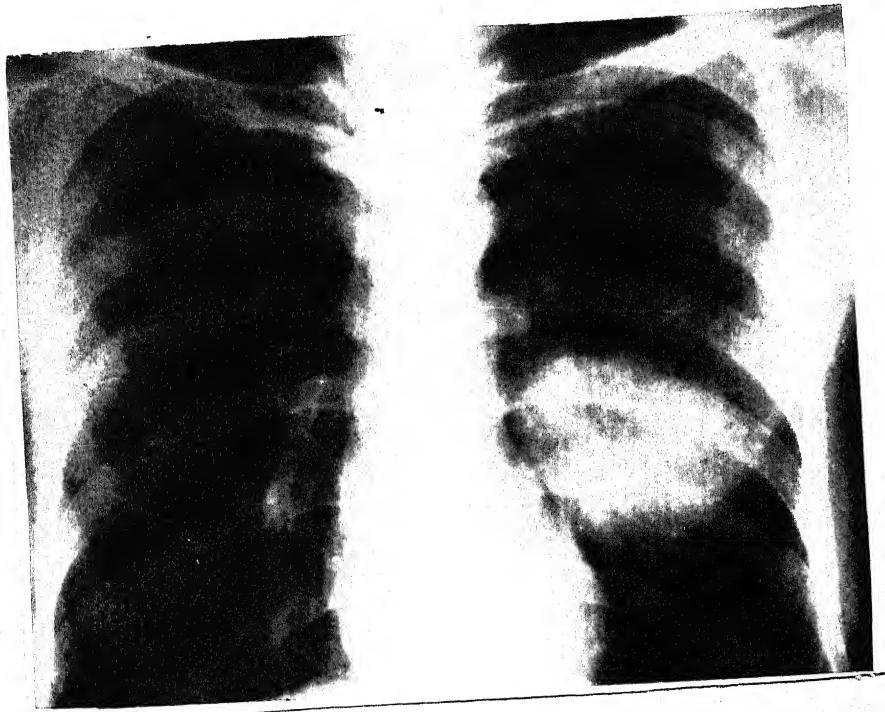


Before Treatment

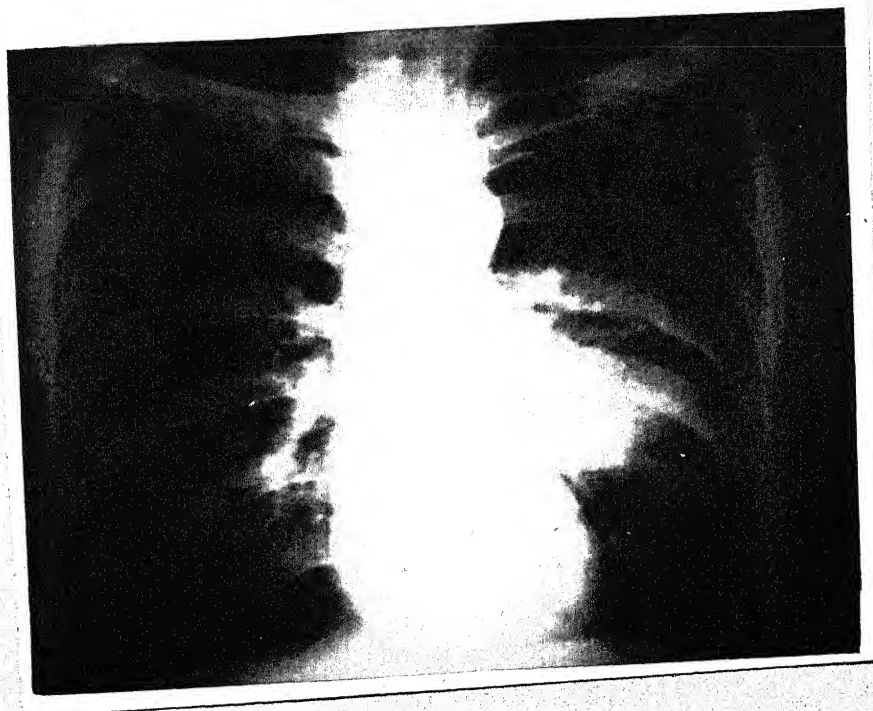


After Treatment

Lung Carcinoma

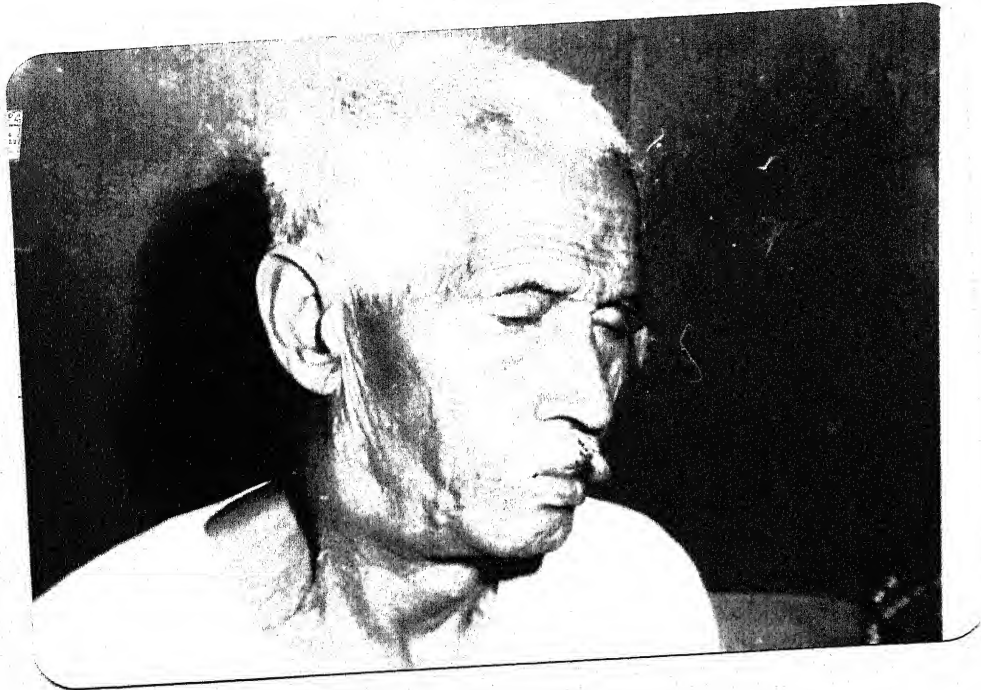


Before  
Treatment

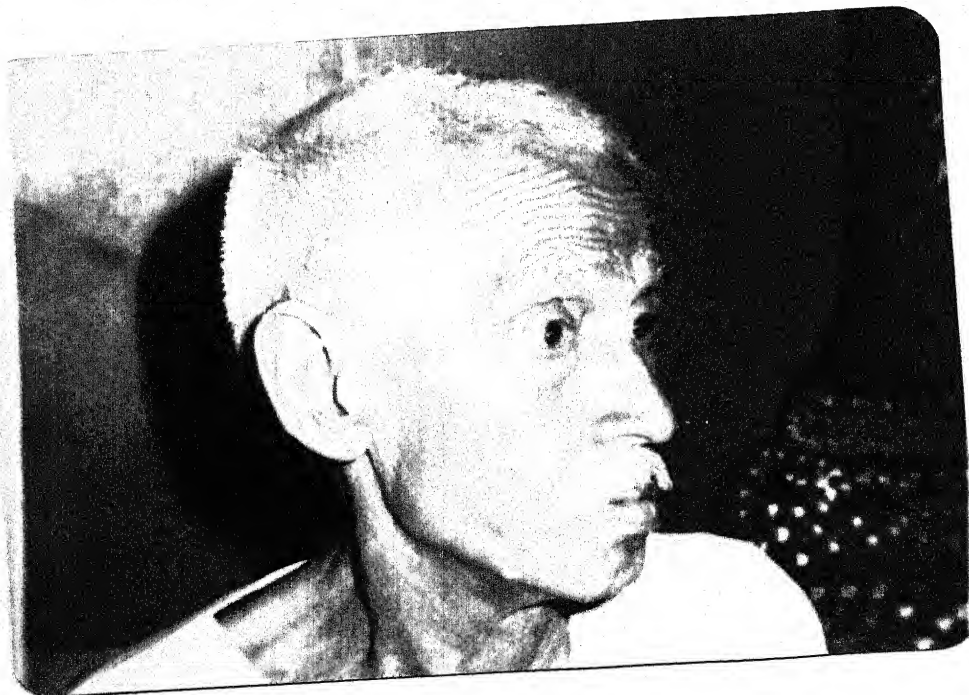


After  
Treatment

Head & Neck Carcinoma



Before  
Treatment



After  
Treatment



Head & Neck Carcinoma



Before  
Treatment



After  
Treatment

Table IX

Early Toxicity		No. of patients	Nausea/vomiting		Fever		Hypersensitivity		Cystitis	
Malignancy			No.	%	No.	%	No.	%	No.	%
Carcinoma Breast	Early	12	5	42.0	-	-	-	-	2	16.6
	Late	5	2	40.0	1	20.0	-	-	-	-
Lymphoma	Hodgkin's	5	2	40.0	-	-	-	-	-	-
	Non-Hodgkin's	7	1	14.0	-	-	-	-	-	-
Leukaemia		8	2	25.0	1	12.5	-	-	-	-
	ALL	1	-	-	-	-	-	-	-	-
	AML	0	-	-	-	-	-	-	-	-
	CLL	5	-	-	-	-	-	-	-	-
Gastro-Intestinal Carcinoma	CML	7	2	28.0	-	-	-	-	1	25.0
	Gastric	4	1	25.0	-	-	-	-	-	-
	Colo-Rectal	4	-	-	-	-	-	-	-	-
	Pancreatic	4	1	20.0	-	-	-	-	-	-
	Gall Bladder & Liver	5	1	33.0	-	-	-	-	-	-
Uro-genital Carcinoma	Ovarian	3	-	-	-	-	-	-	-	-
	Testicular	0	-	-	-	-	-	-	-	-
	Renal	0	-	-	-	-	-	-	-	-
	P prostate	1	-	-	-	-	-	-	-	-
Miscellaneous	Lungs	5	-	-	-	-	-	-	-	-
	Head & Neck	6	1	16.6	-	-	-	-	3	3.8
Total		78	18	23.0	2	2.5	-	-	-	-

## Toxicity

### 1. Early Toxicity -

Nausea or vomiting was seen in 20% to 40% cases of various malignancies and on average it was seen in 23% patients. Fever and Cystitis were observed in 2.5% and 3.8% cases respectively. In no case, hypersensitivity was observed (Table IX).

### 2. Delayed Toxicity - Haematological

Leucopaemia was observed in 12.5% cases of Acute Lymphocytic Leukaemia, but it was not noticed in any other type of malignancy. Thrombocytopaemia was seen in 14% to 25% cases of Lymphoma and ALL. Anaemia was observed in 1 (20%) case of late stage of carcinoma breast and 1 case (12.5%) of ALL. Haemorrhage was noticed in ALL one case (12.5%) and Non-Hodgkins lymphoma one case (14%). On average, Leucopaemia, Thrombocytopaemia, Anaemia and Haemorrhage was observed in 1.28%, 5%, 2.5% and 2.5% cases of all malignancies (Table X).

### 3. Delayed Toxicity - in GIT & Skin

Stomatitis and diarrhoea were observed in one (12.5%) case of ALL. Alopecia in patches was seen in one case (14%) of Non-Hodgkins lymphoma. Hyperpigmentation of skin was not noticed in any case. Overall, stomatitis, diarrhoea and skin pigmentation were seen 1.28% each in malignancies.



Table X

Malignancy	No. of patients	Leucopaenia		Thrombocytopenia		Anaemia		Haemorrhage		
		No.	%	No.	%	No.	%	No.	%	
Carcinoma Breast	Early	12	-	-	-	-	-	-	-	
	Late	5	-	-	-	1	20	-	-	
Lymphoma	Hodgkin's	5	-	-	20	-	-	-	-	
	Non-Hodgkin's	7	-	-	14	-	-	1	14	
Leukaemia	ALL	8	1	12.5	2	25	1	12.5	1	12.5
	AML	1	-	-	-	-	-	-	-	
	CLL	0	-	-	-	-	-	-	-	
	CML	5	-	-	-	-	-	-	-	
	Gastric	7	-	-	-	-	-	-	-	-
Gastro-intestinal Carcinoma	Colo-Rectal	4	-	-	-	-	-	-	-	
	Pancreatic	4	-	-	-	-	-	-	-	
	Gall Bladder & Liver	5	-	-	-	-	-	-	-	
	Ovarian	3	-	-	-	-	-	-	-	
Uro-genital Carcinoma	Testicular	0	-	-	-	-	-	-	-	
	Renal	0	-	-	-	-	-	-	-	
	Prostate	1	-	-	-	-	-	-	-	
Miscellaneous	Lungs	5	-	-	-	-	-	-	-	
	Head & Neck	6	-	-	-	-	-	-	-	
Total	78	1	1.28	4	5	2	2.5	2	2.5	

4. Delayed Toxicity - others

No disorder of nervous system, Renal system, Liver, Heart or Lungs was observed in any case.

5. Death -

Four cases of ALL expired, so mortality in ALL was high (50%). One case diagnosed as chronic myeloid Leukaemia expired. Total mortality was 6.4%.

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DISCUSSION



### DISCUSSION

Present study comprising of 78 diagnosed cases of malignancies, show that breast carcinoma and gastro-intestinal carcinoma (22% and 26% respectively) are the leading types of malignancies. American Cancer Society (1978) has similarly reported that carcinoma of breast (in females 26%), carcinoma of gastro-intestinal tract (13%) and carcinoma of lungs (7 to 22%) are dominant types of malignancies. British data (Kemp and Tome, 1979) also state that frequency of incidence of malignancy in different organs is in order of Lung (in males), breast (in females) and G.I.T.

Agewise, in our study, Lymphomas were found more (50%) in age group of 21 - 30 years. Data from England, United States and Japan, similarly state that Lymphomas are common in young adult life (Peckham, M.J. et al, 1982). Carcinoma of breast is more common (47%) between 41 - 50 years of age. Similar reports have been given by William Duncan (maximum at about 45 years of age) and by UICC (most incidence between 40 - 45 years of age).

In sex-wise distribution of malignancies, our data coincides with reports of UICC (1981) and American Cancer Society (1978). Lymphomas were seen more in males

(75%) than in females (UICC, 1981). In females, breast carcinoma is at the top (42%) which has been mentioned by American Cancer Society (26%) as well as in British data (Kemp and Toms, 1979).

Response rate in the present study for Hodgkin's disease is 75%, while other workers have reported response rate between 90 to 100% (De Vita et al, 1970; Goldsmith et al, 1974) using MOPP Regime. In other clinical trials (Moxley, J. et al, 1967 and Bonadonna et al, 1975) results were 100% and 90% with COMP and ABVD regime respectively. In Non-Hodgkin's lymphoma, overall response remained 40% in comparison to 41 to 50% complete response reported by Luce, J.C. et al, (1971) and Bagley, C.M. et al (1972). Latest trial by Schein et al (1975) and Mc Kelvey, E.M. et al (1975) has improved complete response upto 60% with BACOP and CHOP regime. Thus response rate varied according to the combinations of drugs,

In Acute Lymphocytic Leukaemia (ALL), overall response remained 50% in the present study. Other workers Rodriguez et al, 1973 (64%), Jacquillat et al, 1973 (73%) and Richard Champlin et al (50 to 70%), have reported almost similar results. Response to treatment, in leukaemia, is to be judged in terms of months or years of survival, without disease. In ALL, it is said to be 50% 5-year leukaemia free survival, while in CML average



duration of life from the time of onset is 3 to 4 years. In our study, cases are to be followed for such evaluation of response.

In early breast carcinoma, adjuvant chemotherapy, after surgery, have shown no recurrence or metastasis in any case within this short period of study. Although, relapses (5.3%) have been reported by Bonadonna et al (1975 & 1976) after CMF Regime, but cases are to be followed for long term, to observe 5 year or 10 year disease free survival. Till date, all our patients are enjoying disease free survival. In late stage of breast carcinoma, response rate appeared 33% in our study, while other workers (Broder, L.E., 1974; Canellos, G.P. et al, 1976) reported 50 - 60% response. Various other reports are available regarding the response of chemotherapy in carcinoma breast. Cooper (1969) and Carter, S.K. (1974) have reported response upto 90% with CMFVP (Cooper's) Regime. Latest studies with regimes AC, CAF, PM-FAC and FUVAC by Salmon & Jones (1974), Bull, J. (1977) and Falkson, G. (1985), Martimer, J. et al (1985) and Livingston, R.B. et al (1987) respectively, have shown 70 to 80% response. Besides choice of drugs and dosage, response rate also vary with schedule of drugs.

In Gastric Carcinoma, overall response assessed in our study was 40%, in comparison to other workers (Kazua, O. et al, Moertel, C.G. et al, and Macdonald, J.S. et al).



who obtained response rate 40 to 55%. In Colo-Rectal carcinoma, response rate was 33%, while Baker, L.H. (1975) reported 30% response. In Pancreatic carcinoma, our results show 33% response rate which are almost similar to Carter & Comis, 1975 (30%); Bitran et al, 1979 (40%) and Wiggam, R.G., 1978 (43%). Carcinoma of Gall bladder and liver showed no response in our study in contrast to report by Carter & Livingstone (1970), who obtained 40 to 50% response.

In ovarian carcinoma, partial response was obtained in 50% cases in contrast to 35 to 65% overall response reported by Smith, J.P. et al (1970, 1972), Young, R.C. (1975, 1978, 1984) and Brodovsky, H.S. (1974). Some newer regimes CHAP, CHAD, CAP, Hexa-CAP and CHEX-UP have been worked out by Greco (1981), Vogl, et al (1983), Kane et al (1979) and Young, R.C. et al (1978, 1984) respectively with results 75 to 96%. So ovarian carcinoma is curable if drugs sensitive to malignancy are combined and given in proper dosage and schedule. In Prostatic carcinoma, our study showed partial response in one (100%) case treated with hormones, while Prout, G.R. (1973) has reported 80 to 85% response. If carcinoma prostate prove to be hormone-resistant, cytotoxic drugs alone or along with hormones are given. Such trials give 30 to 38% response (Scott, W.W., 1975; Jonnson, G., 1971; Mittelman, A., 1975) with use of cyclophosphamide, 5 FU or Estracyt (Estradiol-nitrogen mustard combination).

In lung carcinoma, overall response was 25% in comparison to 30 to 55% response reported by Wasserman, T.H. ( 1975), and Bitran et al (1978). Objective response in small cell lung carcinoma has been reported (J. Hopkins, 1979; Einborn, 1979) better (83%) than non-small cell lung carcinoma (48% at Mayo Clinic 1979 and Sloan-Kettering, 1979). In carcinoma of head and neck, we got 40% overall response, while 50 to 80% response has been reported by Cortes, E.P. et al (1972) and Hanham, et al (1971). In long term follow-up, 5-year tumour-free survival has been reported upto 81% (Richards & Chambers, 1973) using hydroxyurea as an adjuvant with surgery and radiotherapy.

Toxic side effects seen in our study varied. Nausea and vomiting, immediate toxicity of almost every cytotoxic drug, was seen in 23% cases. Cystitis found in 3.8% cases was due to cyclophosphamide drug. Leucopaenia (1.28%), Thrombocytopaenia (5%), Anaemia (2.5%) and Haemorrhage (2.5%) were due to Bone marrow depression, which are caused by all cytotoxic drugs. Stomatitis, diarrhoea and alopecia observed in our study may be toxicity of any of the anti-neoplastic drug, e.g. Methotrexate, Flouro uracil, Cyclophosphamide, Vinca alkaloids, or Bleomycin. In our study, Mortality (50%) in cases of ALL was due to severe bone marrow depression.

Though observation period was short and long term follow-up is needed to observe disease free survival, but on the basis of results achieved and comparing the results with other similar studies, it is justified to recommend chemotherapy for cases who either are unfit for surgery or radiotherapy, or where disease has recurred.

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## SUMMARY AND CONCLUSION

### SUMMARY AND CONCLUSION

A prospective study was carried out on 78 cases of malignancy who were admitted in wards of M.L.B. Medical College & Hospital, Jhansi. Chemotherapeutic drugs, single or in combination were given according to different types and stages of malignancies and response of treatment was evaluated.

Malignancies taken for study were Lymphomas, Leukaemias, Carcinoma Breast, Gastro-intestinal Carcinoma, Uro-genital Carcinoma, Lung Carcinoma and Carcinoma of Head & Neck. Response rate in Lymphoma & Leukaemia was 55% and 40% respectively. In breast carcinoma, no metastasis was seen in early stage of carcinoma as a result of chemotherapy and 33% response was seen in late stage of carcinoma breast. In GIT malignancies, overall response appeared 30% and in Urogenital malignancies it was 66%. Response in lung carcinoma was 25% and in Head & Neck malignancies 40%. Thus overall response of chemotherapy varied from 25% to 66% in different malignancies. This variation of response depend not only on combinations of drugs, dosage and schedule, but also on type and sensitivity of malignancies.

Tumours that have not metastasised are amenable to local forms of treatment, surgery or radiotherapy, whilst tumours that have already disseminated or have recurred require systemic treatment with chemotherapy. Failure of surgery or radiation usually results because of metastatic disease rather than failure of local control. Clearly, systemic treatment is needed if we are going to improve the control of such groups of malignancies.

So it is to be admitted that for most of the common forms of malignancies, chemotherapy has much to offer. Chemotherapy can be tried in every form of malignant disease, either localised, disseminated or circulating tumour cells. In some malignancies, chemotherapy contributes to cure, in some effective control of disease, prolongs useful life and in some it is palliative. Thus, chemotherapy in our view is treatment of choice in most of the malignancies.

The truth remains that cancer chemotherapy is of great potential value and needs co-ordinated programmes of multi-modality therapy. The development of effective intermittent combination chemotherapy and its integration with other modalities of treatment such as surgery and radiotherapy has greatly increased the success of our approach to the management of cancer patients and has led to a revolution in the field of cancer research.

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B I B L I O G R A P H Y  
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BIBLIOGRAPHY

1. Adair, FE and Bagg, HT. Experimental and clinical studies on the treatment of cancer by dichloroethyl sulphide (mustard gas). *Annals of Surgery*, 93 : 190-199 (1931).
2. Ahmann, DL, Hann, RG, Bisel, HF et al. A phase II evaluation of ifosfamide (NSC 109729) treatment of disseminated breast cancer. *Proc. Am. Assoc. Cancer.* 15 : 182 (abstr.), 1974.
3. American Cancer Society (1978) : *Cancer Facts and Figures*.
4. Bagley, CM, Devita, VT, Berard, CW, et al : Advanced lymphosarcoma : Intensive cyclical combination chemotherapy with cyclophosphamide, vincristine and prednisone. *Ann. Intern. Med.*, 76 : 227-234, 1972.
5. Baker, LH, Matter, R, Talley, R. et al : 5 FU vs 5 FU and Me-CCNU in gastro-intestinal cancers. A phase III study of the South West Oncology Group. *Proc. Am. Assoc. Cancer Res.*, 16 : 229 (abstr.), 1975.
6. Bergenstal, DM, Hertz, R., Liprett, MB et al. Chemotherapy of adrenocortical cancer with O.P. DDD. *Ann. Intern. Med.*, 53 : 672-682, 1960.
7. Bitran J. et al : CAMP chemotherapy. *Cancer Treat. Rep.*, 60 : 1225, 1976.

8. Bitran, JD, et al. Treatment of metastatic pancreatic and gastric adenocarcinoma with FAM. Cancer Treat. Rep., 63 : 2049-51, 1979.
9. Blokhina NG, Vozny EK and Garin AM : Results of treatment of malignant tumour with Ftorafur. Cancer, 30 : 390-392, 1972.
10. Blum RH, Carter SK and Agre K : A clinical review of bleomycin - a new antineoplastic agent. Cancer, 31 : 903, 1973.
11. Bonadonna G, Zucali R, Monfardini S, et al : Combination chemotherapy of Hodgkin's disease with adriamycin, bleomycin, Vinblastine and Imidazole carboxamide versus MOPP. Cancer, 36 : 252-259, 1975.
12. Bonadonna G, et al : Adjuvant CFM Chemotherapy in inoperable breast cancer. Ten year later. Lancet, 1 : 976, 1985.
13. Bonadonna G. et al : The CMF programme for operable breast cancer with axillary nodes. Updated analysis on the disease free interval site of relapse and drug tolerance. Cancer, 39 : 2904-15, 1977.
14. Bonadonna G, Brusamolino E, Valaguna P, et al : Combination chemotherapy as an adjuvant treatment in operable breast cancer. N. Eng. J. Med., 294 : 405-440, 1970.



15. Bonadonna G and Valaguna P. Dose response effect of adjuvant chemotherapy in breast cancer. *New England J. Med.*, 304-10-15, 1981.
16. Bonadonna G, Monfardini S, De Lena M. et al : Clinical evaluation of Adriamycin, a new antitumour antibiotic. *Br. Med. J.*, 3 : 503-506, 1969.
17. Bonadonna G, Brusamolino E, Valagussa, P. et al : Adjuvant study with combination chemotherapy in operable breast cancer. *Proc. Am. Assoc. Cancer Res.*, 16 : 254, 1975.
18. Bonadonna G, Zuceli R, De Lena, M and Valagussa P : Combined chemotherapy (MOPP or ABVD) radiotherapy approach in advanced Hodgkins disease. *Cancer Treatment Reports*, 61 : 769-777, 1977.
19. Border LE, Caster SK : Pancreatic islet cell carcinoma : Results of therapy with streptozotocin in 52 patients. *Ann. Intern. Med.*, 79 : 109-118, 1973.
20. Braim Lillo C, De Lena M and Bonadonna G : Combination chemotherapy with Adriamycin (NSC - 123127) in metastatic mammary carcinoma. *Cancer Chemother. Rep. Part - I*, 58 : 251, 1974.
21. Broder LE and Tormey DC : Combination chemotherapy of carcinoma of the breast. *Cancer Treatment Reviews*, 1 : 183-204, 1974.
22. Broome JD : Studies on the mechanism of tumour inhibition by L-asparaginase. *J. Exp. Med.*, 127 : 1055, 1968.

23. Bull J, Newer combination chemotherapy trials in advanced breast cancer. Perspectives in the treatment of breast cancer. 1976. Ann. Intern. Med., 86 : 784-98, 1977.
24. Burchenal JH and Karnofsky DA : Clinical evaluation of L-asparaginase. Cancer, 25 : 241-243, 1970.
25. Burchenal J. et al : Clinical evaluation of a new antimetabolite - 6-mercaptopurine. In the treatment of Leukaemia and allied disease. Blood, 8 : 965-999, 1953.
26. Burchenal JH, et al : Studies on the chemotherapy of Leukaemia. Cancer, 1 : 399, 1948.
27. Caley WB : The treatment of malignant tumors by repeated inoculation of erysipelas with a report of ten original cases. Am. J. Med. Sci., 105 : 487, 1893.
28. Cancellas GP, Pocock SJ, Taylor SG et al : Combination chemotherapy for metastatic breast carcinoma. Cancer, 38 : 1882-1886, 1976.
29. Cancellors GP, Young RC, Nieman P. et al : Dibromo mannitol in the treatment of chronic granulocytic leukaemia. A prospective randomized comparison with busulfan. Blood, 45 : 197-203, 1975.
30. Cancellas GP, et al : Combination chemotherapy for advanced breast cancer response and effect on survival. Ann. Intern. Med., 84 : 389-92, 1976.



31. Canellos GP, Pecoock SJ, Taylor SG, et al : Combination chemotherapy for metastatic breast carcinoma. *Cancer*, 38 : 1882-1886, 1976.
32. Carter SK and Livingstone R : Single agents in cancer chemotherapy. Plenum Publishing Corporation, New York, Pages 217-218, 1970.
33. Carter SK : The chemical therapy of breast cancer seminars in Oncology, 1 : 131, 1974.
34. Carter SK : The chemical therapy of breast cancer with a combination of adriamycin and cyclophosphamide. *Proc. Am. Assoc. Cancer Res.*, 15 : 90, 1974.
35. Carter SK and Comis Rh : The integration of chemotherapy into a combined modality approach for cancer treatment VI, Pancreatic adenocarcinoma. *Cancer Treat. Rev.*, 2 : 193-194, 1975.
36. Carter SK and Slavik M : Investigational drugs under study by the United States National Cancer Institute. *Cancer Treatment Review*, 3 : 43-60, 1976.
37. Carter SK : The integration of chemotherapy into combined modality treatment of solid tumor. VII Adenocarcinoma of the breast cancer treatment Reviews, 3 : 141-174, 1976.
38. Carter SK and Sober WT : Integration of chemotherapy into combined modality treatment of solid tumors : I. The overall strategy, *Cancer Treatment Reviews*, 1 : 1-13, 1974.



39. Carter SK, Comis RL : The integration of chemotherapy into a combined modality approach for cancer treatment VI Pancreatic carcinoma. Cancer Treatment Reviews, 2 : 193-214, 1975.
40. Chawla PL, Lokich JJ, Jaffe, N. et al : Phase I study of cyelo cytidine 0-2-2'-cyclocytidine hydrochloride. Proc. Am. Assoc. Cancer Res., 15 : 188 (Abstr.), 1974.
41. Chemotherapy Statistical Unit - Surgical adjuvant Breast Study-I. Progress Report, 1964, Buffalo, New York, Roswell Park Memorial Institute.
42. Cheng E. et al : VAB II in metastatic testicular cancer. Cancer, 42 : 2162, 1978.
43. Cohen FB - Lippman AJ, Custodio MC and Dexter JA : New antineoplastic drugs and their proper use. Medical Clinics of North America, 60 : 959-970, 1976.
44. Coher MH and Mittelman A : Initial clinical trials with isofosfamide. Proc. Am. Assoc. Cancer Res., 14 : 64 (Abstr.), 1973.
45. Cook WL Jr, Sciforth WJ and Kastlin GJ : The use of nitrogen mustard in malignant disease. Am. Pract. & Digest Treat., 1 : 785, 1950.
46. Cooper R : Combination chemotherapy in hormone resistant breast cancer. Proc. Am. Assoc. Cancer Res., 10 : 15, 1969.

47. Corter EP, Shedd D, Albert DJ, Ohnuma T and Hreshchyshyn M : Adriamycin and bleomycin in advanced cancer.  
Proc. Am. Assoc. Cancer Res., 13 : 86, 1972.
48. Cvitkovic E, Currie V, Krakoff IH et al : Bleomycin infusion with CTS platinum di ammine dichloride as secondary chemotherapy for germinal cells tumors.  
Proc. Am. Assoc. Cancer Res., 16 : 273 (Abstr.), 1975.
49. Davis HL, Ramirez G, Elles by RA and Ansfield FJ : Five drug therapy in advanced breast cancer, factor influencing toxicity and response. Cancer, 34 : 239, 1974.
50. Deleno M, Brainhill C, Morabito A. et al : Adriamycin Vincristine compared to and combined with cyclophosphamide, methotrexate and 5 FU in treatment for advanced breast cancer. Cancer, 35 : 1107-1108, 1975.
51. De Vita V, Serpick A and Carbone P : Combination chemotherapy in the treatment of advanced Hodgkin's disease. Ann. Intern. Med., 73 : 881-895, 1970.
52. De Vita VT and Schein PS : The use of drugs in combination for the treatment of cancer. Rationale and results.  
New England Journal of Medicine, 288 : 998-1006, 1973.
53. De Vita VT, Serpick AA and Carbone PP : Combination chemotherapy in the treatment of advanced Hodgkin's disease. Annals of Intern. Medicine, 73 : 881-1035, 1970.



54. Di Marco A, Gactani M, Dorigotti L, Soldati M and Bellini O : Experimental studies on the antitumour activity of daunomycin : A new antibiotic with antitumour activity. *Tumour's*, 49 : 203, 1963.
55. Donohue JP : CTS diammine dichloroplatinum, vinblastine and bleomycin combination chemotherapy in disseminated testicular cancer. *Ann. Intern. Med.*, 87 : 293, 1977.
56. EASTERN CO-OPERATIVE ONCOLOGY GROUP (ECOG) : Performance status scale and DA KARNOFASKY et al. *Cancer*, 1 : 634, 1948.
57. Editorial : A sparaginase. *Medical Journal of Australia*, 2 : 1045-1046, 1971.
58. Binhorn LH, Furnas BE, Powell N : Combination chemotherapy of disseminated testicular carcinoma with Cis-platinum diammine dichloride (CPDD), Vinblastine VLB and bleomycin (BLEO). *Am. Soc. Clin. Oncol.*, 17 : 240, 1976.
59. Elson LA, Jarman M and Ross WCJ : Toxicity, Haematological effects and antitumor activity of epoxides derived from disubstituted hexitols. Mode of action of mannitol myleran and dibromomannitol. *Eur. J. Cancer*, 4 : 617-625, 1968.
60. European Organization for Research on the Treatment of Cancer, Clinical Screening of epipodophylotoxin Vm 26 in malignant lymphomas of solid tumor. *Brit. Med. J.*, 2 : 744-748, 1972.



61. Evans JS, Musser BA, Mengel GD, Forsblad KR and Hunter JH :  
Anti-tumour activity of 1B-D arabinofuranosyl cytosine  
hydrochloride. *Prof. Soc. Exp. Biol-Med.*, 106 : 350,  
1961.
62. Falkson G, Gelman RS, Tarmey DC, Cummings FJ, Carbone PP  
and Falkson HC. The eastern co-operative Oncology.  
Group experience with cyclophosphamide Adriamycin and  
5 FU (CAF) in patients with metastatic breast cancer.  
*Cancer*, 56 : 219-224, 1985.
63. Farber S. Chemotherapy in the treatment of Leukaemia and  
Wilms tumor. *JAMA*, 198 : 826-836, 1966.
64. Farber S, Diamond LK, Mercer RD, Sylvester RF and  
Welff JA. Temporary remission in acute Leukaemia in  
children produced by folic acid antagonist, 4 amino  
pteroyl-glutamic acid (aminopterin). *New England Journal  
of Medicine*, 238 : 787-793, 1948.
65. Farber S (ed.). Second Conference on Folic acid antagonist  
in the treatment of Leukaemia, Boston, March 11, 1951,  
*Blood*, 7 : 97, 1952.
66. Farber S, D'Angio GT, Evans AE, et al : Clinical studies  
of Actinomycin D with special reference to Wilm's tumour  
in children. *Ann. N.Y. Acad. Sci.*, 89 : 423-424, 1960.
67. Fisher B. et al : L Phenylalanine Mustard (L-PAM) in the  
management of primary breast cancer - an update of earlier  
findings and a comparison with those using L-PAM & 5 FU.  
*Cancer*, 39 : 2883-903, 1977.

68. Fisher B, Raudin RG, Ausman RK et al. Surgical adjuvant chemotherapy in cancer of breast. Result of a decade of co-operative investigation. *Ann. Surgery*, 168 : 337-356, 1968.
69. Frank W, Osterberg AE : Mitomycin C (NSC-26980) - An evaluation of the Japanese reports. *Cancer Chemother. Rep.*, 9 : 114-119, 1960.
70. Freireich DJ, Karon M and Frei E : Quadruple combination chemotherapy (VAMP) for acute lymphocytic leukaemia of childhood. *Proceedings of the American Association for Cancer Research*, 5 : 20, 1964.
71. Friedman M, De Narves FN and Daly JP. Treatment of squamous cell carcinoma of the head & neck with combined methotrexate and irradiation. *Cancer*, 25 : 711, 1970.
72. Frytak S, Moertel CG, Schutt AJ et al. A Phase I study of Cytembena. *Proc. Am. Assoc. Cancer Res.*, 16 : 36 (Abstr.) 1975.
73. Gee TS, Yu KP and Clarkson ED : Treatment of adult acute Leukaemia with arbinosyl cytosine and thioguanine. *Cancer*, 23 : 1019, 1963.
74. Gilman A. The initial critical trial of nitrogen mustard. *Am. J. Surg.*, 105 : 574, 1963.
75. Goldsmith MA and Carter SK. Combination chemotherapy of advanced Hodgkin's disease - a review. *Cancer*, 33 : 1-8, 1974.



76. Goldsmith MA and Carter SK : The integration of chemotherapy into a combined modality approach to cancer therapy. V Squamous cell cancer of the head and neck. Cancer Treatment Review, 2 : 137-158, 1975.
77. Goodman LS, Wintrobe MM, Dameshek W, Goodman MJ, Gilman A, and Mc Lennan MT. Nitrogen Mustard therapy. Journal of the American Medical Association (JAMA), 132 : 126-132, 1946.
78. Gottlieb JA, Freireich EJ, Bodey GP et al : Preliminary clinical evaluation of piperazinedione (P), a new crystalline antibiotic. Proc. Am. Assoc. Cancer Res., 16 : 86 (Abstr.), 1975.
79. Gottlieb J, Hill C, Ibanez M. et al : Chemotherapy of thyroid cancer. Cancer, 30 : 848-853, 1972.
80. Gottlieb JA and Drewinko B : Review of current clinical status of platinum co-ordination complexes in cancer chemotherapy. Cancer chemotherapy Reports, 59 : 621-628, 1975.
81. Greenspan E : Response of advanced breast cancer to the combination of the antimetabolite, methotrexate and alkylating agent. Thio TEPA J Mt. Sinai Hosp., 30 : 246-267, 1963.
82. Haddaw A and Timmis GM : Myleran in chronic myeloid leukaemia. Chemical constitution and biological action. Lancet, 1 : 207, 1953.



83. Haller D. et al : FAM for advanced colo-rectal and pancreatic cancer. Pract. Am. Ass. Cancer Res. Am. Soc. Clin. Oncol., 19 : 342, 1978.
84. Hanham IW, Newton KA and Westbury G : Seventy five cases of solid tumour treated by a modified quadruple chemotherapy regime. Br. J. Cancer, 25 : 462, 1971.
85. Hansen H, Muggia FM, Andrew R and Selaury OS : Intensive combined chemotherapy and Radiotherapy in patient with non-resectable bronchogenic carcinoma. Cancer, 30 : 315, 1972.
86. Heidal-Rerger C and Ansfield PJ. Clinical and experimental use of fluorinated pyrimidines in cancer chemotherapy. Cancer Res., 23 : 1226, 1963.
87. Henderson EB : Combination chemotherapy of acute lymphocytic leukaemia of childhood. Cancer Research, 27 : 2570-2572, 1967.
88. Henderson EB : Treatment of acute Leukaemia. Seminar in Haematology, 6 : 271-319, 1969.
89. Herbert WP : Effects of estradiol dipropionate and diethyl stilbestrol on malignant prostate tissue. Trans. Am. Assoc. Genitourin. Surg., 34 : 195, 1941.
90. Higgins GA. Jr. Use of chemotherapy as an adjuvant to surgery for bronchogenic carcinoma. Cancer, 30 : 1383, 1972.

91. Hill BT and Baserga R : The cell cycle and its significance for cancer treatment. *Cancer Treatment Reviews*, 2 : 159-175, 1975.
92. Hodes ME, Rohn RJ and Bond WH : Vincalukoblastine I Preliminary clinical studies : *Cancer Research*, 20 : 1041-1049, 1960.
93. Ho DH, Rodriguez V, Cottlieb JA et al : Pharmacologic and dose ranging studies of cyclocytidine CC in man. *Proc. Am. Assoc. Cancer Res.*, 14 : 93 (abstr.), 1974.
94. Holden WD, Dixon WJ and Kuzma JW : Adjuvent chemotherapy for colo-rectal carcinoma. In Cole. WH (ed.) *Chemotherapy of cancer*. Philadelphia, Lea & Febiger, 1970, P. 312.
95. Holden WD and Dixon WJ : A study of the uses of Triethylene, thiophosphamide as an adjuvent to surgery in the treatment of Colo-rectal cancer. *Cancer Chemotherapy Rep.*, 16 : 129, 1962.
96. Huggins, C and Hodges CV : Studies on prostatic cancer. The effect of castration of estrogen and of androgen injection on serum phosphatase in metastatic carcinoma of the prostate. *Cancer Res.*, 1 : 293, 1941.
97. Jacquillet, C, Weil M and Gemon MF : *Cancer Res.*, 33 : 3278-84, 1973.



98. Jacobson LO, Spurr CL, Barron ESG, Smith T, Lushbaugh C and Dick GF. Nitrogen mustard therapy : studies on the effect of methyl - bis (B-chloroethyl) - amine hydrochloride on neoplastic disease and allied disorders on the haemopoietic system. JAMA, 132 : 263, 1946.
99. Johnson IS, Armstrong JG, Gorman M and Burnett JP. Jr. The Vinca alkaloids, a new class of oncolytic agents. Cancer Res., 23 : 1390, 1963.
100. Kaufman JH, Mittelman A : Phase I study of inosine dialdehyde (diglycoaldehyde NSC 118994). Proc. Am. Assoc. Cancer Res., 16 : 51 ( abstr.), 1975.
101. Kazuo O, Kurita S and Nishimura M : Combination therapy with mitomycin C, 5 fluorouracil and cytosine arbinoside for advanced cancer in man. Cancer Chemother. Res., 56 : 373-385, 1972.
102. Kemp NH and Toms J : Cancer statistics, 1977, In Cancer Research Campaign, 56th Annual Report, 1978, 54-65.
103. Kennedy BJ and Yarbrow JW : Metabolic and therapeutic effects of Hydroxyurea in chronic myeloid Leukaemia. JAMA, 195 : 1038-1043, 1966.
104. Kovach JS and Meertel CG : A phase I study of chloromycin A<sub>2</sub> (toyomycin) therapy. Proc. Am. Assoc. Cancer Res., 14 : 23 (abstr.), 1973.



105. Kovach JS, Moertel CG, Ahmann DL, et al : Phase I study of chloromycin A<sub>2</sub> (NSC - 58514). Cancer Chemother. Rep., 57 : 341-347, 1973.
106. Krum Bhaer EB. Role of the blood and bone marrow in certain forms of gas poisoning. JAMA, 72 : 39, 1919.
107. Lacher M and Durant J : Combined vincristine and chlorambucil therapy of Hodgkin's disease. Ann. Intern. Med., 62 : 468-476, 1965.
108. Lacher M and Durant J : Combined vincristine and chlorambucil therapy of Hodgkin's disease. Ann. Intern. Med., 62 : 468-476, 1965.
109. Laing AH, Berry RJ, Newman CR and Smith P : Treatment of small cell carcinoma of bronchus. Lancet, i : 129, 1975.
110. Li Mc, Whitmore WF, Golbey R. et al : Effects of combined drug therapy on metastatic cancer of the testis. JAMA, 74 : 1291-1299, 1960.
111. Lipshutz H. and Lerner HJ : Six year survival in the combined treatment of far advanced head and neck cancer under a combined therapy programme. Am. J. Surg., 126 : 519, 1973.
112. Lissauer in Benderf Zwei, Falls, Von Leucemie. Berl. Klin. Wochr. Vol. 2, No. 40, 403, October 2, 1865.

113. Livingstone RB et al : Combination chemotherapy and systemic irradiation combination for poor prognosis breast cancer. *Cancer*, 59 : 1249-1254, 1987.
114. Leerer AA : Mammary carcinoma. Response to implantation of male hormone and progesterone. *Lancet*, 2 : 698, 1941.
115. Longmire WP, Kisma JW and Dixon WJ : The use of Triethylene thiophosphoramide as an adjuvant to the surgical treatment of gastric carcinoma. *Ann. Surg.*, 167 : 293, 1965.
116. Luce JC, Gamble JF, Wilson E. et al : Combined cyclophosphamide, vincristine and prednisone therapy of malignant lymphoma. *Cancer*, 28 : 306-317, 1971.
117. Luce JK, Thurman WG, Isaacs BL. et al : Clinical trial with the antitumour agent. 5-(3,3-Dimethyl-1-Triazeno). Imidazole-4-Carboxamide (NSC 45388). *Cancer Chemother. Rep.*, 54 : 119-124, 1970.
118. Mac donald JS et al : 5 FU, Doxorubicin (Adriamycin) and Mitomycin (FAM) : Combination chemotherapy for advanced gastric cancer. *Ann. Intern. Med.*, 93 : 533-536, 1980.
119. Mackenzie AR : Chemotherapy of metastatic testis cancer. Results in 154 patients. *Cancer*, 19 : 1369-1375, 1966.
120. Martin DS : The necessity for combined modalities in cancer therapy. *Hospital Practice*, 8 (1) : 129, 1973.



121. McKelvey EM, Gottlieb JA, Haut A. et al : Hydroxyl daunomycin (adriamycin) combination chemotherapy in non-Hodgkin's lymphoma. Proc. Am. Assoc. Cancer Res., 16 : 233 (abstr.), 1975.
122. Mertimer J, Flournoy N, Livingstone RB and Stephens RH : Aggressive Adriamycin - containing Regimen (PM-FAC) in estrogen receptor - negative disseminated breast cancer. Result of South West Oncology Group Trial. Cancer, 56 : 2376-2380, 1985.
123. Moertel CG et al : Phase II study of Me-CCNU in the treatment of advanced pancreatic carcinoma. Cancer Treat. Rep., 60 : 1659-61, 1976.
124. Moertel CG, Mittelman JA, Bakemeier RF et al : Sequential and combination chemotherapy of advanced gastric cancer. Cancer, 38 : 678-682, 1976.
125. Moertel CG : Therapy of advanced gastro-intestinal cancer with the nitrosoureas. Cancer Chemother. Rep., 4 : 27-34, 1973.
126. Moertel CG et al : A clinical trial of amygdalin (Lactrile) in the treatment of human cancer. N. Eng. J. Med., 1982, 306 : 201.
127. Moertel CG and Reitemeier RJ : Advanced Gastro-intestinal cancer. Cancer - clinical Management and Chemotherapy, New York, Harper & Row (1969).



128. Moxley J, De Vita V, Bruce K. et al : Intensive combination chemotherapy and X-irradiation in Hodgkin's disease. *Cancer Res.*, 27 : 1258-1263, 1967.
129. Mrazek RG, Economou SG, McDonald GO, Slaughter DP and Cele WH : Prophylactic and adjuvant use of Nitrogen mustard in the surgical treatment of cancer. *Ann. Surg.*, 150 : 745, 1959.
130. Muggia F, Selowry O and Hanson A : Clinical studies with a new podophyllotoxin, derivative epipodophyllotoxin, 4'-demethyl-9 (4,6-O2-benzylidene-B-D-Glucopyranoside) (NSC-122819). *Cancer Chemotherapy Rep.*, 55 : 575-581, 1971.
131. Nissen-Meyer R. et al : Surgical adjuvant chemotherapy. Result of one short course of cyclophosphamide after Mastectomy for breast cancer. *Cancer*, 41 : 2080-90, 1978.
132. Noer RJ (Chairman Surgical Adjuvant Chemotherapy Breast Group). Breast Adjuvant Chemotherapy : Effectiveness of Thio TEPA as Adjuvant to Radical Mastectomy for Breast Cancer. *Ann. Surg.*, 154 : 629, 1961.
133. Peckham MJ et al : Treatment of cancer (Edited by Keith E. Halnan) Page 692, 1982.
134. Pratt C, Rivera G and Shanks E : Phase III evaluation of piperazinedione in children with cancer. *Proc. Am. Assoc. Cancer Res.*, 16 : 82 (abstr.), 1975.

135. Prout GR : Prostate gland. In Halland JP, Frie E (eds.) : Cancer Medicine, Philadelphia, Lea & Febiger, 1973, PP 1680-1694.
136. Ramirez G : Five drug combination therapy in the treatment of solid tumours. Proc. Am. Assoc. Cancer Res., 14 : 17, 1973.
137. Reitemeier RJ, Moertel CG and Hann RC : Combination chemotherapy in Gastro-intestinal cancer. Cancer Res., 30 : 1425-1428, 1970.
138. Rerenberg B : Possible mechanisms for the antitumour activity of platinum co-ordination complexes. Cancer chemotherapy Reports, 59 : 589-598, 1975.
139. Reni Anna et al : Multimodal treatment in operable breast cancer : Five year results of the CMF programme. Br. Med. J., 198 : 1427-31, 1981.
140. Rhoads CP : Nitrogen mustard in the treatment of neoplastic disease. JAMA, 131 : 656, 1946.
141. Richard Champlin, David W Golde : The Leukaemia, Harrison's Principles of Internal Medicine (1987), Page 1546, 1987.
142. Rodriguez V. et al : Cancer, 32 : 69-75, 1973.
143. Rodriguez V, Gottlieb JA, Burgess MA et al : Clinical studies of Baker's antifol (BAF). Proc. Am. Assoc. Cancer Res., 16 : 83 (abstr.), 1975.

144. Selmon SE and Jones SE : Chemotherapy of advanced breast cancer with a combination of adriamycin and cyclophosphamide. *Proc. Am. Assoc. Cancer Res.*, 15 : 90, 1974.
145. Samuels ML, Johnson DS and Holoye PY : The treatment of stage III metastatic germinal cell neoplasia of the testis with bleomycin combination chemotherapy. *Proc. Am. Assoc. Cancer Res.*, 14 : 23 (abstr.), 1973.
146. Samuels ML : Continuous Intravenous bleomycin therapy with Vinblastin in testicular and extragonadal germinal tumours. *Proc. Am. Assoc. Cancer Res.*, 16 : 112 (abstr.), 1975.
147. Schein P, De Vita VT, Canellos G. et al : A new combination chemotherapy programme for diffuse histiocytic and mixed non-Hodgkin's lymphoma. *Proc. Am. Assoc. Cancer Res.*, 16 : 248 (abstr.), 1975.
148. Schein PG, Chabner BA, Canellos GP. et al : Results of combination chemotherapy of Non-Hodgkin's lymphoma. *Br. J. Cancer*, 31 (Suppl.) II : 465-473, 1975.
149. Schulk G : Erfahrungen mit neuen cytostatischen Mitteln bei Hamoblastosen und carcinomen und die Abgrenzung ihrer Wirkungen gegen Rontgentherapie. *Z - Krebsforsch.*, 58 : 500, 1952.



150. Silvey O, Yagoda A, Wittes R. et al : Treatment of germ cells carcinomas with a combination of actinomycin D, Vinblastine and bleomycin. Proc. Am. Assoc. Cancer Res., 14 : 59 (abstr.), 1973.
151. Skeel R, Rodriguez V, Freireich EJ et al : Clinical and pharmacological studies of the folate antagonist, triazinate (Baker's antifol T2T). Proc. Am. Assoc. Cancer Res., 15 : 77 (abstr.), 1974.
152. Sklensky B, Mann Kaplan R, Reynolds et al : 4' De methyl, Epipodophyllotoxin-B-D Themylidene glucoside (PTG) in the treatment of intracranial neoplasm. Phase II. Cancer Chemotherapy Rep., 57 : 91, 1973.
153. Slavik M, Carter SK : Bronchogenic carcinoma - New drugs available for study. Cancer Chemotherapy Rep., 4 : 265-269, 1973.
154. Smith JP, Rutledge F : Chemotherapy in the treatment of cancer of ovary. Amer. J. Obstet. Gynecol., 107 : 681-703, 1970.
155. Smith JP, Rutledge F and Wharton JT : Chemotherapy of ovarian cancer : new approaches to treatment. Cancer, 30 : 1565-1571, 1972.
156. Apierr ASD : Experience with procarbazine in the treatment of acute leukaemia and other neoplasms. Medical Journal of Australia, 2 : 732-735, 1967.

157. Spitz S : The mitological effects of nitrogen mustards on human tumors and tissues. *Cancer*, 1 : 343, 1948.
158. UICC : Manual of Cancer Chemotherapy, 1981.
159. Vasantha Kumar AR, Renandin J, Wilson CB et al : Procarbazine hydrochloride in the treatment of brain tumour - Phase-2 study. *J. Neuro surgery*, 40 : 365-371, 1974.
160. Vincent T, De Vita JR : Principles of Cancer Therapy. *Harrison's Principles of Internal Medicine* (1987) : Page 441, 1987.
161. Vogler WR, Miller D and Keller JW : Remission induction in refractory myeloplasic leukaemia with continuous infusion of 5 azacytidine. *Proc. Am. Assoc. Cancer Res.*, 16 : 155 (abstr.), 1975.
162. Vurgin D et al : VAB-6 combination chemotherapy in disseminated cancer of the testis. *Ann. Intern. Med.*, 95 : 59, 1981.
163. Waksman SA (Ed.) : The actinomycins and their importance in the treatment of tumours in animals and man. *Ann. N.Y. Acad. Sci.*, 89 : 283, 1960.
164. Warwick OH, Darte JPM and Brown TC : Some biological effects of vinca leukoblastine, an alkaloid in *Vinca rosea* Linn in patients with malignant disease. *Cancer Research*, 20 : 1032-1040, 1960.



165. Wassermann TH, Comis RL, Goldsmith M et al : Tabular analysis of the clinical chemotherapy of solid tumour. Cancer Chemother. Rep., 6 : 399-419, 1975.
166. Wiggins KG et al : Phase II trial of SMF in the treatment of advanced pancreatic cancer. Cancer, 41 : 387-391, 1978.
167. William Duncan : Treatment of Cancer (Edited by Keith E. Holman) Page 329, 1982.
168. Wilson WL, Birel HF, Cole D. et al : Prolonged low dosage administration of hexa-methyl melamine (NSC 13875). Cancer, 25 : 568-570, 1970.
169. Wintrobe MM et al : Nitrogen mustard as a therapeutic agent for Hodgkin disease lymphosarcoma and leukaemia. Ann. Intern. Med., 27 : 529, 1947.
170. Witter RE et al : Chemotherapy of germ cell tumour of the testis. Cancer, 37 : 637, 1976.
171. Young RC : Chemotherapy of ovarian cancer : past and present. Semin. Oncol., 2 : 267-276, 1975.
172. Young RC : Ovarian carcinoma. Sem. Oncol., 9 : 209, 1984.

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